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PULMONARY TUBERCULOSIS IN HARVARD MEDICAL STUDENTS*

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DESPITE the marked fall in recent years in the morbidity and mortality due to pulmonary tuberculosis and despite advances in its early diagnosis and treatment, tuberculous infection of the lung remains the most serious medical problem that confronts the medical student. Although for more than a century European clinicians had been aware of an apparent high incidence of pulmonary tuberculosis among medical students, it was not until 1930 that Steidl[1] called to the attention of American clinicians the fact that a similar high incidence was being overlooked in American medical schools. Stimulated by Steidl's report, Hetherington and his co-workers[2] conducted a survey showing that over 20 per cent of the senior class at the University of Pennsylvania Medical School had what they considered to be significant adult-type pulmonary tuberculosis. This alarming report stimulated the undertaking of surveys at other medical schools. In 1939 Soper and Amberson[3] reviewed information collected from surveys made at the medical schools of the universities of Pennsylvania, Wisconsin and Oslo and of Johns Hopkins, Yale, Columbia, Harvard, Stanford and New York universities and at the Woman's Medical College. The incidence reported from these schools varied from 0.4 per cent (Columbia) to 13.5 per cent (University of Pennsylvania). Since Soper and Amberson's report surveys have been conducted at Cornell[4], Northwestern[5] and New York universities.[6]

As might be expected, there was significant variation in the rates at various schools, depending on the geographical origin of the student body, the location of the school, the diagnostic criteria and the care with which the survey was conducted. Many schools, particularly in the early reports, found that the previously known incidence tripled or quadrupled when formal case-detecting programs were instituted. Other factors, such as the irregular occurrence of epidemics of tuberculosis in certain highly susceptible or heavily exposed classes, occasionally operated to produce unduly high figures. Furthermore, some of the high incidences reported in the earlier papers appear to be partly based on the presence of lesions that would now be considered obsolete tuberculosis of no clinical importance. It was presumably a combination of many such factors that produced the uniquely high figures at the University of Pennsylvania — a rate rarely even approached in the experience of other schools. Most carefully conducted surveys report an incidence in the neighborhood of 1 or 2 per cent.

In the light of present knowledge, it is the purpose of this paper to review and analyze the material on pulmonary tuberculosis that has accumulated in the records of the health office at Harvard Medical School during the last twenty-three years. In so doing an endeavor will be made to trace the steps that led to the evolution of the case-finding program now employed at Harvard Medical School.

MATERIAL AND METHODS

The data presented in this study were obtained chiefly from a search of the records kept by the physicians to students at Harvard Medical School.§ The medical histories of twenty-four classes, beginning with the class of 1926, were studied. All available clinical information in the files of the Health Office, as well as sanatorium reports and personal communications, was reviewed in each case. The x-ray films available in 23 cases were reviewed, with special attention to the extent and location of the lesions.

In all cases presented in this study chest films showed either the appearance of a lesion not previously present or extension of a previously known

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§These records were kept by Drs. Reginald Fitz, Clark Heath, Eugene Eppinger, Lewis Dexter and Lewis Kane.

lesion. Calcified primary complexes, however extensive, thickened apical caps, blunted costophrenic angles and small apparently obsolete nodules were not considered clinically significant, and are not included in any of the tabulations or discussions. Supporting clinical evidence for activity included at least one of the following characteristic symptoms: cough, hemoptysis, fever, anorexia, weight loss and general malaise. In many cases acid-fast bacilli were demonstrated in the sputums, gastric washings or pleural effusions, either by direct observation or by guinea-pig inoculation.

The tuberculin-test figures were derived from the original work sheets of the routine tuberculin surveys. The two-test-dose, intradermal method was used, the results being read in forty-eight hours. Induration of at least 5 mm. in diameter was used as the sole criterion of a positive test. No student was considered a nonreactor unless the full strength of the second dose — 1.0 mg. O.T. (Old Tuberculin) or 0.005 mg. P.P.D. (Purified Protein Derivative) — had been given. Classes 1936 through 1940 and the Class of 1941 during its first three years were tested with O.T.; all subsequent classes were tested with P.P.D.

From 1922, when records were first kept, until 1932 no routine case-detection program was employed. In the latter part of this period, however, more than four hundred chest x-ray films were taken on the basis of weight loss, history of contact, suggestive symptoms or suspicious signs.[7] The first routine case-detection program, which was adopted in 1932, consisted of intradermal tuberculin tests and x-ray examination of the chest for all members of the entering classes and also for many members of the graduating classes. In 1936 the plan was extended to include annual tuberculin retesting of all nonreactors, and all positive reactors were encouraged to have annual x-ray examinations of the chest.[8] The present method was adopted in 1943, although it did not have complete application until 1944. Routine tuberculin tests and x-ray examinations of the chest were done on all members of the entering classes. The students were then re-examined semiannually — tuberculin reactors by x-ray and nonreactors with tuberculin. Although the semiannual rule was not effectively enforced until 1944, its official adoption in the preceding year led to virtually complete participation of the student body in at least one routine examination in that year; participation had previously been wide but not complete.

Results

X-ray Findings

From 1922 through 1945, a total of 44 students were known to have developed active pulmonary tuberculosis on the basis of the criteria outlined above. The x-ray films were available for study in 23 cases; in the remainder the information was gleaned from the repofts of the radiologist.* Most of the lesions were in the apical or subclavicular areas. A characteristic position was the outer portion of the second anterior interspace, as pointed out by Sosman.[9] About 70 per cent were minimal (National Tuberculosis Association classification[10]), and the remainder moderately advanced. There were no known far advanced lesions in the initial x-ray films. Demonstrable cavitation was rare, occurring in only 3 cases. Four cases that developed in medical school and had apparently inactive lesions in the x-ray films on admission are included in this study because none of the lesions appeared to be a direct recurrence of a previous one. In 2 cases of massive pleural effusion without demonstrable parenchymal involvement, acid-fast organisms were demonstrable in the pleural fluid.

Incidence

Of 3160 students in Classes 1926 to 1948, it is known that 44 developed pulmonary tuberculosis — an over-all incidence of 1.4 per cent. Because of the relative inefficiency of the case-finding program prior to 1936, however, the actual rate of the disease was undoubtedly considerably greater. Thus Classes 1926 to 1932, in which no organized case-finding program was conducted, had an incidence of 0.9 per cent. Classes 1933 to 1936 had routine chest films and tuberculin tests on admission, and many, but not all, students had chest films in their fourth year; in this group the incidence was 1.1 per cent. These figures may be contrasted with those for Classes 1937 to 1943, in which routine chest x-ray examination and tuberculin tests on admission were followed by annual re-examination of all nonreactors by the tuberculin test and of most positive reactors by x-ray examination, and in which the rate was 2.2 per cent. The apparent variation in incidence, correlated with the type of case-finding program, is given in Table 1.

Table 1. *Incidence of Tuberculosis according to Type of Case-Detecting Procedure.*

Classes	Procedure	No. of Students*	No. of Cases	Incidence %
1926–1932	Symptoms and physical examination	893	8	0.9
1933–1936	Entrance tuberculin test and x-ray examination, with (recommended) repetition at graduation	496	6	1.2
1937–1945	Annual tuberculin test and (recommended) x-ray examination of reactors	1153	25	2.2
1946–1948†	Semiannual tuberculin test or x-ray examination	—	5	—

*Corrected for second-year and third-year transfers.
†These classes have not yet completed medical school.

*All films were originally examined or later reviewed by Dr. Merrill C. Sosman at the Peter Bent Brigham Hospital.

The demonstration of an incidence almost three times that known before the introduction of a case-finding program is in accord with the experience of other medical schools. At the universities of Minnesota,[11] Wisconsin[12] and Pennsylvania[2] and at Yale University[13] the introduction of case-finding programs increased the previously known rate between four and six times.

Development of Tuberculosis according to Academic Year

The academic year in which the lesion was first discovered is known in 34 of the 44 cases and is listed in Table 2. The fourfold increase in the number of cases appearing in the last two academic years, as compared with the first two, is discussed below. A similar finding has been reported from other medical schools.[2, 5, 6, 14]

TABLE 2. *Cases of Tuberculosis according to Academic Year of Appearance.*

Year of Appearance	No. of Cases
On entrance	5
First	1
Second	5
Third	11
Fourth	12
Total	34

Significance of Tuberculin Reaction

The tuberculin reaction on entrance to medical school was known in 26 cases prior to the development of the pulmonary lesion. Sixteen students were positive reactors, and 10 were nonreactors. Of the former, 3 were found to have active lesions on x-ray examination at entrance; 13 positive reactors and 10 nonreactors developed lesions during medical school. Since Classes 1936 to 1948 included 51.7 per cent positive reactors and 48.3 per cent nonreactors on entrance, the ratio of 13 positive reactors to 10 nonreactors suggests that the nature of the tuberculin reaction on entry had little influence on the development of active pulmonary tuberculosis in medical school.

On the other hand, conversion from nonreactive to reactive state while in medical school carried a definite liability. In Classes 1936 to 1947 there were 188 students who were nonreactors on entrance but who subsequently became reactors while in medical school. Of these, 10 (5.3 per cent) developed active pulmonary tuberculosis in medical school, and at least 3 others developed parenchymal or pleural tuberculosis soon after graduation. Information on the status of the remainder of the group after graduation is too fragmentary to permit estimation of a postgraduate incidence.

Three students who developed clinical pulmonary tuberculosis were known to have been nonreactors five, eleven and eleven months before the diagnosis was established. The importance of this fact in determining the proper timing of the interval when routine x-ray examination or tuberculin tests should be performed is discussed below.

No case of pulmonary tuberculosis was found in any student with a negative tuberculin reaction. The number of positive reactors, if any, who became nonreactors during medical school is unknown, since positive reactors were not retested. In nonmedical groups it has been shown that a small but significant number of reactors lose their reactive state during varying periods of observation.[15, 16]

Classification of Pulmonary Lesions

The extent and intensity of the pulmonary lesions were classifiable in 26 of the 31 cases in classes 1936 to 1948. On the basis of the National Tuberculosis Association criteria,[10] 18 were minimal lesions, and 8 were moderately advanced. Cavitation was rare, being demonstrable in only 3 cases.

Since most of the lesions were minimal all were subgrouped according to the classification of Sampson[17] in use at the Trudeau Sanatorium, which is based on intensity (chiefly density) of the lesion, as well as on its area. Intensity A is slight, B is moderate, and C represents consolidation, cavity or dense fibrosis. Any of these intensities may be applied to a minimal, moderately advanced or far advanced lesion. When the 26 cases were so reclassified, 13 appeared as minimal of A intensity and constituted the minor-lesion group. Thirteen others appeared as minimal of B or C intensity or as moderately advanced of A, B or C intensity, constituting the major-lesion group. Pleural effusions were classified as major lesions.

TABLE 3. *Disability according to Severity of Lesion.*

Character of Lesion	Total No. of Cases	No. of Cases Needing Sanatorium Care	Average Sanatorium Stay	No. Withdrawing from Medical School
			mo.	
Minor	13	6	14	1*
Major	13	11	30	3

*Because this student had diabetes mellitus and active pulmonary tuberculosis on entry, he was advised to withdraw.

Confirming the validity and prognostic value of this grouping was the marked difference in degree and duration of disability between the categories. Of the 13 cases comprising the minor-lesion group, 7 students did not require sanatorium care. For the 6 requiring sanatorium care, the period of hospitalization varied from ten to twenty months, with an average of fourteen months. Two of these

6 are still in sanatoriums — 1 for six months and the other, now about to return to school, for twenty months. On the other hand, of the 13 cases in the major-lesion group, only 2 students did not require sanatorium care. Of the 11 who entered sanatoriums, 3 failed to return to medical school (after five, five and two years). The remaining 8 students spent from one to five years in sanatoriums before returning to medical school, averaging over thirty months of hospitalization (Table 3).

The minor lesions, however, were not so innocuous as these figures suggest. One student with a minor lesion developed a small new lesion shortly after returning to school following twelve months of sanatorium care. Also, at least 2 students with minor lesions considered not to require hospitalization subsequently developed, during internship, reactivations severe enough to require sanatorium care.

Table 4. *Severity of Lesion according to Number of Cases Developing in Each Academic Year.*

Type of Lesion	Academic Year of Development				
	on entrance	first	second	third	fourth*
Minor	4	0	2	4	3
Major	1	1	2	7	2

*The severity of many of the lesions developing in the fourth year could not be classified because of missing films.

No clear-cut correlation could be found between the severity of the lesion and the academic year of discovery or between the severity and the original tuberculin reaction (Tables 4 and 5).

On the other hand, correlation between severity of the lesion and method of detection was striking. Of the 31 cases in Classes 1936 to 1948 the method of detection is known in 25. Thirteen were found on routine chest x-ray examination, and 12 only after the appearance of suggestive symptoms. Of the former, 1 was classified as major and 12 as minor, and in the 12 detected on the basis of symptoms the distribution was directly reversed, 11 being major and 1 minor (Table 6). All 11 major cases discovered on the appearance of symptoms occurred prior to the institution of the semiannual routine examinations; 5 students were tuberculin reactors on entrance, 5 were nonreactors, and 1 was not tested because of a known previous lesion. Four of the 5 reactors had negative chest films on entry and were therefore subject only to voluntary annual examination before their fourth year. All 4 developed symptoms in their third year. By means of the annual tuberculin retesting of negative reactors, it was possible to determine the interval between a previous negative reaction and the onset of symptoms. Of the 5 nonreactors in the annual retest who developed tuberculosis, 3 developed symptoms within a year (five, eleven and eleven months); 2 developed symptoms four and eleven months after the annual tuberculin test had shown a positive reaction.

Table 5. *Severity of Lesion according to Tuberculin Reaction on Entrance.*

Type of Lesion	No. of Positive Reactors	No. of Nonreactors
Minor	7	3
Major	6	5

Table 6. *Severity of Lesion according to Number of Cases Discovered by Two Methods.*

Type of Lesion	Discovered on Routine X-ray Examination*	Discovered by Symptoms
Minor	12	1
Major	1	11

*A routine x-ray film is one taken at stated periodic intervals or because of a recently acquired positive tuberculin reaction discovered in the routine surveys.

The contrast between the results of the program of voluntary annual x-ray examination and those of the present compulsory annual and more recent semiannual examination is striking: since the institution of the present program there have been 5 cases of pulmonary tuberculosis, 4 of which were detected by routine chest film and tuberculin test and 1 following a hemoptysis; all 5 students had minor lesions.

Table 7. *Severity of Lesions according to Number of Cases Detected by Annual and Semiannual Case-Finding Programs.**

Type of Lesion	Annual Examination	Semiannual Examination
Minor	8	5
Major	13	0

*The case-finding program refers to that in operation at the time the lesion was detected. It does not consider the actual method of detection of the individual lesions, many of which were recognized by the appearance of symptoms despite the program in force at the time.

A breakdown of the 26 cases of known severity according to the program in force at the time of detection is given in Table 7. The elimination of the previously preponderant major cases under the present regime is noteworthy.

Tuberculin Test

Tuberculin tests on entrance showed an average of 51.7 per cent of students to be reactors (Table 8). A steep downward trend, leveling off or perhaps even reversing in recent years, presumably represents a lowering of tuberculous infection in the college-age population, associated with a decrease

in tuberculosis in the general population. A similar decreasing incidence of positive reactors during approximately the same period has been noted among students entering college[19] and other medical schools.[14]

The rate of conversion of nonreactors to reactors while in medical school is shown in Table 9. Except for the third-year and fourth-year tests on Classes 1944 and 1945, the retests were done in the first two months of each academic year, and the results were therefore largely the effects of the preceding year. Although the significance of the class variation (24 per cent for the Class of 1941 and 47 per cent for the Class of 1937) remains speculative, the high level of these attack rates is noteworthy. If one assumes that the acquisition of the reactive state represents tuberculous infection, approximately 34 per cent of students became infected during medical school.

By means of the annual tuberculin test it was possible to determine an annual attack rate for each class. Although there was considerable variation from class to class, the average attack rates for each academic year showed surprisingly little variation. For the six classes 1940 through 1945, the rates were as follows: second-year test 12 per cent; third-year test 13 per cent; and fourth-year test 13 per cent (Table 10). The relation between this remarkable constancy in attack rate per year and the preponderance of pulmonary tuberculosis in the last two academic years is discussed below.

TABLE 8. *Tuberculin Reactions on Entrance.*

CLASS	NO. OF STUDENTS	NO. OF STUDENTS TESTED	NO. OF REACTORS	PERCENTAGE OF REACTORS
1936	123	120	84	78
1937	125	124	101	81
1938	124	118	78	66
1939	126	122	74	61
1940*	125	124	62	50
1941	125	125	74	59
1942	126	123	52	42
1943	128	128	43	34
1944	127	125	66	53
1945		124	56	45
1946a		123	54	44
1946b		122	40	33
1947		112	45	40
1948		110	50	45
Average				52

*The O.T. used for this class was subsequently reported to be of substandard potency by Seideman.[18]

DISCUSSION

Pulmonary tuberculosis is the most serious medical problem that confronts the health departments of medical schools. Since the institution of an efficient case-finding program, the known incidence at the Harvard Medical School has been 2.2 per cent. Of special importance are cases with more than minor pulmonary lesions. Students with such major lesions have had prolonged periods of disability, averaging over two and a half years of absence from medical school. In addition, several failed to complete their medical education. Almost without exception, students whose lesions were detected by the appearance of symptoms showed major lesions, whereas just as regularly students whose lesions were detected by routine examination showed minor lesions. Only about half the students with minor lesions required sanatorium care. The average stay of those who required such care was fourteen months.

The demonstrable effectiveness of routine examination in the detection of early lesions makes frequent examination mandatory. The original case-finding program at Harvard Medical School, consisting of routine tuberculin tests and chest x-ray examination on entry and at graduation, has been progressively modified to the present semiannual examination. During the period of annual examination one of us (H.P.B.[20]) was able to show, on the basis of the existing Harvard Medical School material, that when routine chest x-ray examinations were done only annually or approximately annually, a large proportion of the lesions became symptomatic, and were thereby detected, before the time of re-examination. In addition, at least 3 students developed major lesions within a year of having been found to be nonreactors in the annual test.

Since major lesions often develop within a year after infection or after a negative chest x-ray examination, it is our belief that six months represents the maximum interval that should be allowed to elapse between routine x-ray examination of tuberculin reactors and tuberculin tests of nonreactors. When students previously nonreactors become reactors in the semiannual examination, x-ray examination of the chest should probably be done every six weeks for six months, and every three months for the remainder of the year. The use of this case-finding routine examination has, so far, eliminated the previously preponderant major

TABLE 9. *Cumulative Attack Rates of Entrance Nonreactors Who Became Positive Reactors during the Second, Third or Fourth Year.**

CLASS	PERCENTAGE
1936	36
1937	47
1938	38
1939	33
1940	41
1941	24
1942	32
1943	27
1944	41
1945	28

*In Classes 1936 to 1939, the rates are based on a single fourth-year test of entrance nonreactors. In classes 1940 to 1945, the rates are based on accumulation of reactors in annual and semiannual retests of entrance nonreactors.

lesions and virtually eliminated the cases detected on the basis of symptoms. Since the institution of the present program, there have been 5 cases of pulmonary tuberculosis, 4 of which were detected by the routine examination and 1 by the occurrence of hemoptysis. All 5 were minor lesions. If the asymptomatic cases had been allowed to continue until a later examination, or until the development of overt symptoms, it is not inconceivable that some students would have developed major lesions.

By means of the annual tuberculin test it was possible to determine the number of students who became infected each academic year. It was anticipated that more students would become tuberculin reactors during the clinical years, owing to greater exposure on the wards and in the autopsy room. Badger and Spink[21] estimate that over 600 tuberculous patients are admitted annually to the general wards of one teaching hospital in Boston. At the same hospital 7 per cent of all autopsies performed up to 1941 showed active tuberculosis as a primary or contributing cause of death.[22] Heavy contamination of air near tables where fresh tuberculous tissue is examined has been repeatedly demonstrated.[23] In New York State 10 per cent of all deaths from tuberculosis occur in general hospitals,[24] and in Massachusetts, Dufault[22] has estimated the figure at 20 per cent.

Despite greater opportunity for infection during the clinical years, an unexpected constancy in the attack rate (12 to 13 per cent) was found for each academic year. This uniformity indicates that there is equal opportunity for infection throughout each year. The predominance of cases of pulmonary tuberculosis in the third and fourth years has always been explained by greater exposure during those years. The constancy in annual attack rate seems to argue against greater exposure as the sole cause of the predominating number of cases during the clinical years; it is well known that factors other than opportunity for exposure operate in determining whether tuberculosis develops. A possible explanation is the accumulation of recently infected students whose primary lesions remain quiescent until clinical training is begun, when the lesions become reactivated because of the longer and irregular hours of physical and mental exertion. It must also be kept in mind that each academic year the medical student enters an age group whose mortality and estimated morbidity rate become increasingly high.[25] Unfortunately no adequate figures are available for the incidence of tuberculosis among carefully studied groups of the same age who are subject to the same conditions of living as well as to physical and mental exertion. As Rich[25] has emphasized, in none of the published studies of graduate students in nonmedical fields are diagnostic criteria, thoroughness of study and duration of survey completely satisfactory. Only when adequate long-term surveys are made may one safely estimate the special risk of tuberculosis among medical students as contrasted with that among comparable groups of students not pursuing medical studies.

The lack of correlation between the nature of the original tuberculin reaction and the probability that active pulmonary tuberculosis will develop in medical school is of considerable interest. Experimentally it has been demonstrated that a previous infection offers some degree of protection against a subsequent infection under some conditions,[26, 27] but offers undue susceptibility under others.[28, 29] Furthermore, aside from such acquired resistance or hypersensitivity, it might be expected that fewer cases would appear among tuberculin reactors because this group has been challenged and has weathered the infection, whereas the nonreactor group has yet to demonstrate its native resistance. Such factors might be balanced by the possibility of endogenous recurrence in the reactor group. Reports in the literature on the incidence of tuberculosis in exposed groups of reactors and nonreactors vary from a greater incidence in the former[30, 31] to a greater incidence in the latter,[32, 33] or show no appreciable difference in the two groups. In the present study, the absence of appreciable difference between groups suggests that the nature of the original reaction presumably played only a minor role under the conditions studied.

TABLE 10. *Annual Attack Rates according to Classes.*

CLASS	SECOND-YEAR TEST				THIRD-YEAR TEST				FOURTH-YEAR TEST			
	NO. OF NONREACTORS	NO. RETESTED	NO. OF REACTORS	PERCENTAGE OF REACTORS	NO. OF NONREACTORS	NO. RETESTED	NO. OF REACTORS	PERCENTAGE OF REACTORS	NO. OF NONREACTORS	NO. RETESTED	NO. OF REACTORS	PERCENTAGE OF REACTORS
1940	62	62	7	11	55	52	7	13	45	45	11	24
1941	51	49	4	8	45	45	5	11	40	39	3	8
1942	71	71	6	8	65	61	11	18	50	50	5	10
1943	85	83	12	14	71	69	6	9	63	47	5	11
1944*	59	59	10	17	49	44	8	18	36	33	5	15
1945*	68	65	7	11	58	58	6	10	52	46	5	11
Totals		389	46			329	43			260	34	
Averages				12				13				13

*The third-year and fourth-year figures for these two classes are based on two tests, made six months apart.

SUMMARY AND CONCLUSIONS

The application of efficient case-detection methods shows that pulmonary tuberculosis in medical stu-

dents remains a major medical problem. The incidence of significant active adult-type pulmonary tuberculosis in Harvard Medical School was 2.2 per cent.

Although the nature of the tuberculin reaction of medical students on entrance played no demonstrable role in the subsequent development of pulmonary tuberculosis, the conversion from the nonreactive to the reactive state while in medical school carried a liability greater than 5 per cent that the disease would develop before graduation.

Slightly over 30 per cent of students who entered Harvard Medical School as nonreactors became tuberculin reactors before graduation.

Although the number of cases of pulmonary tuberculosis discovered in the last two years of the medical-school course was four times as great as the number developing in the first two years, the incidence of acquisition of tuberculous infection was about the same (12 or 13 per cent annually) for each academic year. This constant annual attack rate suggests that factors other than opportunity for infection are responsible for the fourfold increase in cases of pulmonary tuberculosis during the term of clinical training.

The duration of disability caused by the pulmonary lesion was closely correlated with the severity of the lesion at the time of its discovery.

Lesions detected by the appearance of symptoms were of greater severity and carried a far greater period of disability than those discovered by any routine method.

The rapidity of progression of the disease in medical students is such that many lesions become symptomatically evident, and are thereby detected, in intervals between routine examinations made only annually.

The adoption of a program in which surveys are made at intervals more frequent than once a year led to the elimination of almost all symptom-detected cases and of all major lesions. It is our belief that a semiannual examination represents the maximum interval for routine re-examination by x-ray examination or tuberculin tests not only for medical students but also for nurses and interns.

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DYSPEPSIA, ULCER AND GASTRIC CANCER*

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IN 1928 Sir Berkeley Moynihan[1] wrote, "Not a little of the incredulity of patients and the apathy of medical men is based upon the undisputed conviction that cancer of the stomach is incurable." When it is realized that under the favorable circumstances existing in large metropolitan hospitals only 5 of every 100 patients who apply for treatment are cured of their disease, this becomes understandable, perhaps, but is still not justifiable. It is an undoubted fact that most practitioners of medicine have never seen a cured case of gastric cancer but that they have seen large numbers of patients die of the disease. When one recalls that this disease accounts for a third of all deaths from cancer, numbering approximately 40,000 cases yearly in this country, no further argument regarding its importance appears to be necessary.

The insidious character of gastric cancer is often put forward as the reason for this pessimistic picture, and although it is unquestionably true that in a small percentage of patients the disease is beyond the possibility of surgical extirpation when the first symptom manifests itself, study of the clinical histories reveals that in most cases symptoms have been present for months or years before the diagnosis is established. The culpability for this delay in establishing the diagnosis rests not only on the patient who fails to seek medical advice during the early stages of the disease but also in large measure on the physician who is satisfied to treat the patient medically for months or years without benefit of the searching investigation that is imperative in all such cases.

As Mullen[2] has pointed out:

> It is an unfortunate fact that most persons consider a mild degree of gastric discomfort to be a normal part of the process of growing older, and the words "indigestion" and "dyspepsia" to most minds signify an uncomfortable but entirely benign process. Yet within these two words lies the whole story of early gastric cancer symptomatology.

It is also true that this attitude is shared in large measure by many physicians.

The significant factor that is clearly responsible for the delay in the diagnosis of gastric cancer is the unfortunate circumstance that early cancer of the stomach shares with benign gastric lesions and functional disorders the symptoms of dyspepsia or indigestion as an early manifestation. This dyspepsia may be indefinite, or may simulate to a slight or marked degree or may mimic exactly the syndrome associated with benign peptic ulcer. The resemblance of gastric cancer to the classic ulcer syndrome has been general knowledge for many years. In 1906 Graham[3] wrote as follows: "In the later nineties our attention was strongly attracted by the many long histories of 'dyspeptic trouble' that preceded cancer of the stomach, and the thought that ulcer was this precancerous condition became firmly implanted." In 1909 Moynihan[4] reported that 2 of every 3 patients with cancer of the stomach on whom he had operated had had a previous history of ulcer. Despite the fact that these observations were made forty to fifty years ago, their implications have not been widely appreciated or seen in proper perspective in relation to their obvious bearing on early diagnosis. The more recent literature continues to emphasize the frequency of ulcer or symptoms of ulcer in the clinical histories of patients with cancer of the stomach. Blackford[5] reported that 38 per cent of his patients presented histories of preceding ulcer, and Eusterman[6] stated that in 47 per cent of proved cases of gastric cancer encountered at the Mayo Clinic, the history was that of the accepted syndrome of benign ulcer. Whether the natural course of the disease in these cases is a degeneration of a previously benign ulcer or peptic ulceration of a slowly growing cancer or a prolonged precancerous state, distinct from ulcer, is a matter of secondary importance. The significant point is that in a substantial percentage of cases a long history exactly mimics or closely resembles the accepted syndrome of ulcer.

The present study is based on the records of 192 patients with carcinoma of the stomach seen in private practice and at the Massachusetts Memorial Hospitals. Since the majority of these patients were referred for consideration of surgical treatment, these cases represent a selected series, and this fact is reflected in a somewhat higher resectability rate than is usually reported. Seventy-seven cases were suitable for resection—a rate of 41 per cent. Twenty of these, however, were palliative resections, and 57 were resections for cure—in the latter group, the resectability rate was 30 per cent. Thirty-three cases were classed as inoperable, 60 were found to be inoperable on exploration, 18 were suitable for palliative procedures only, and 20 were suitable for palliative resections; 4 patients refused operation. Thus, in a relatively favorable, somewhat selected series of 188 patients in whom the ultimate status was determined, 111 (70 per cent) were hopeless when first seen by the surgeon.

Long delay before the diagnosis was established was almost the rule. The average delay before the

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patient sought medical advice was nine months, and the total average delay for all cases before the diagnosis was established was seventeen months. There was a delay of from one to three months in 52 cases, including a few in which there was a delay of less than a month. There was an average delay of four to six months in 39 cases, of seven to twelve months in 48 cases, of thirteen to twenty-four months in 23 cases, of twenty-five to forty-eight months in 8 cases, of forty-nine to sixty months in 8 cases, and of sixty to one hundred and thirty-two months in 14 cases.

The relative culpability of patient and physician for the delay could not be established in all cases, but in 127 cases the patient was responsible for an average delay of nine months, and in 72 cases the blame for an average delay of seventeen months rested on the physician.

In 46 cases, or 24 per cent, the first x-ray examination failed to establish the diagnosis. A diagnosis of ulcer was rendered in 28 cases (14 per cent), with a resultant average delay of fourteen months before the final diagnosis was made, although 6 of these patients were operated on immediately. A diagnosis of ulcer with a question of cancer was made in 6 cases (3.1 per cent), with a resultant average delay of almost three months, although 3 of the 6 patients were operated on immediately. In 10 cases (5.2 per cent) a report of no disease was rendered, with a resultant delay of fifteen months. In 1 case a diagnosis of diverticulum of the stomach was made, and in another a diagnosis of gall-bladder disease. Both patients were subjected to immediate operation.

Study of the clinical histories in these cases revealed that epigastric pain or burning, epigastric distress or fullness and indigestion were the first symptoms in 131 (70 per cent) of the series. Anorexia occurred in 17 per cent, weakness or fatigue in 14 per cent, vomiting in 10 per cent, weight loss in 7 per cent, dysphagia in 6 per cent, and hematemesis in 5 per cent.

In 17, or 8.8 per cent, a history of typical ulcer was given, and in 52 (27 per cent) a history suggestive of ulcer was obtained, making a total of 69, or 36 per cent, in which the ulcer syndrome was reproduced or suggested.

The implications of this analysis are clear. Apart from the failure of the patient to seek medical advice, a major source of error contributing to delay in establishing the diagnosis of cancer of the stomach is an astonishing degree of willingness on the part of physicians to treat, without x-ray examination or other investigation, patients in the cancer age group who have indigestion, epigastric pain or distress. From a study of the histories in these cases, it seems clear that patients whose symptoms were suggestive of ulcer were treated on that basis, and that those whose symptoms were so indefinite as to suggest insignificant functional disorders were treated by various forms of dietotherapy and usually with alkaline powders. This casual method of dealing with such complaints has become widely known to the public and, in combination with advertisements for patent remedies, is undoubtedly a factor in the high incidence of self-treatment.

There is obviously a great lack of appreciation of the serious import of such symptoms in persons past the age of forty-five, and insufficient familiarity with the frequency with which such symptoms herald the presence of cancer, on a purely statistical basis.

Rivers,[7] in a significant paper, has emphasized the fact that indigestion occurring in patients over forty-five years of age is frequently due to cancer. In an analysis of 2448 patients in various age groups who presented themselves with the symptom of indigestion, cancer of the stomach was found to be the cause in 8.8 per cent of patients from forty-five to forty-nine, in 10.8 per cent of those from fifty-five to fifty-nine, in 24 per cent of those from sixty to sixty-four, and in 36 per cent of those over seventy.

It is difficult to believe that anyone familiar with these figures would be willing to risk treatment of a patient with dyspepsia without benefit of searching investigation. It is essential that this information be disseminated, and it is necessary to reiterate that dyspepsia in patients over forty-five is a grave symptom.

Another source of error is an exaggerated notion regarding the accuracy of roentgenologic diagnosis. It is often stated that intragastric lesions can be accurately diagnosed in 90 to 95 per cent of cases. On inquiry, however, it seems clear that this high degree of accuracy is attainable only in large centers, where roentgenologists of exceptional experience and skill are available, and even then only when questionable cases are subjected to repeated examinations. This is not to decry the great value of roentgenographic diagnosis, but it is essential to point out that, in the hands of the average roentgenologist, such accuracy in diagnosis is not approached. In this series there were wrong diagnoses in 24 per cent, and Engel[8] has stated that in this type of examination there is an admitted error of 20 to 25 per cent. In any patient in whom the diagnosis of gastric cancer is suggested, repeated x-ray examination at short intervals is imperative if the patient's symptoms persist.

The differential diagnosis of gastric ulcer and ulcerating gastric cancer merits special consideration. In fact the whole question of the management of gastric ulcer needs to be reviewed. A growing body of evidence suggests that there is an irreducible error in the neighborhood of 10 to 14 per cent in the roentgenologic diagnosis of this disease. Kirklin,[9] emphasizing a point that is obviously not appreciated by the average clinician, writes as follows:

Such ulcers designated as benign, without qualifying adjectives are designated so — but with the implication that as no marks of malignancy are discerned, the lesions are probably benign, although malignancy cannot be positively excluded. The fact that 10 per cent or more of gastric ulcers are found microscopically to be malignant has been publicized thoroughly, and the roentgenologist feels that his diagnosis may not have been misleading, for he assumes that every ulcer will be considered as potentially malignant until proved innocent.

It is undoubtedly on the basis of this apparently irreducible error in roentgenologic interpretation that Allen and Welch[10] found carcinoma in fourteen per cent of 277 cases diagnosed as ulcer. Judd and Priestley,[11] in a similar series of 237 cases in which a diagnosis of benign gastric ulcer was made, found cancer on exploration in 19 (8 per cent) and in 146 cases diagnosed as benign ulcers that were treated medically, 10 per cent of patients subsequently developed gastric cancer. The wisdom of treating medically any lesion that carries a 10 to 14 per cent chance of being malignant seems open to serious question. The approach of Judd and Priestley[11] in evaluating the relative risks attending medical versus surgical treatment for lesions diagnosed as gastric ulcer seems to go far toward clarifying this sharply debated subject. In a further analysis of 146 cases treated medically, they found that only 47 per cent of patients considered themselves cured; an additional 16 per cent had no symptoms if the medical regime was followed constantly, 5 per cent had gastric ulcer on x-ray examination, 11 per cent were operated on because of failure of medical treatment and had ulcer, and 10 per cent (14 patients) presented definite evidence of cancer. Of these, 7 died of metastatic cancer; the remainder were explored surgically, and in only 3 could the cancer be removed. In contrast, of 162 patients with gastric ulcer treated surgically who were followed for from one to five years, only 1 classified the result as unsatisfactory.

In the past few years there have been increasing reports of large series of gastric resection for benign ulcers of the stomach and duodenum, with mortality rates well under 5 per cent. Counseller, Waugh and Claggett,[12] Judd and Priestley,[11] Jordan and Lahey,[13] and St. John[14] reported rates of 1.3, 2.5, 2.7 and 3 per cent respectively, and McKittrick, Moore and Warren[15] reported a series of 94 cases without a death.

If one assumes that the results of surgical treatment are at least as good as those of medical treatment, with an operative mortality of 3 to 4 per cent, and balances against this the facts that with medical treatment 10 to 14 per cent of patients develop cancer and that a significant percentage have perforations and serious hemorrhages, — some of whom die, — it seems difficult to escape the conclusion that gastric ulcer, at least in patients over the age of forty-five or fifty, should be considered primarily a surgical problem. Of course each case is an individual problem, and exceptions should be made in patients who, because of advanced age, obesity or coexisting disease, must be regarded as poor surgical risks. Certainly, a more radical attitude toward this disease will yield a significant increase in the percentage of cured gastric cancer, for Allen and Welch[10] have shown that the cure rate for cancers encountered in operation on supposed ulcers is double the prevailing rate. The advantages resulting from the greater use of surgery in dealing with ulcerating gastric lesions, of course, depend on the maintenance of a low operative mortality. Rates such as those cited above can be expected only in the hands of experienced gastric surgeons.

In a certain percentage of ulcerating gastric lesions, the roentgenologist makes a diagnosis of gastric ulcer but suggests that cancer cannot be ruled out. In such cases the patient is frequently subjected to a therapeutic trial on medical treatment, the clinical response being observed, the stools watched for the presence or absence of occult blood, and after an interval of two or three weeks the change in the roentgenographic picture noted. This method of management is advocated by most gastroenterologists, including Jordan[16] and Eusterman,[17] who states that the results of medical treatment are only slightly less decisive than those of operation and histologic examination in establishing the diagnosis of ulcer or cancer. My experience with therapeutic trial, as well as that of many others, does not support this belief. Ulcerating cancers often respond so favorably — both clinically and in the rapid diminution of the size of the ulcer — as to lead one to the conviction that the lesion was benign. At best, when the result of therapeutic trial suggests that the lesion is malignant and operation is advised, a delay of from four to six weeks or longer is frequent.

The chief objection to the therapeutic method, however, is that the end results do not bear out the contention of those who advocate it: Eusterman[17] reports the development of cancer in 10 per cent of medically treated ulcer cases not limited to patients in the cancer age or to patients in whom the suspicion of cancer is greater than average.

To one accustomed to dealing with cancer, a diagnostic method that depends for its success on observing the continued growth or persistence of a malignant tumor, in spite of treatment for weeks, has little to recommend it; such a procedure may have been amply justified when gastric resection carried an operative mortality of from 15 to 20 per cent, but with a mortality in the neighborhood of 3 per cent, the risk of medical treatment of a malignant tumor must be carefully weighed.

A hopeful fact is that much of the delay in the diagnosis of gastric cancer is susceptible of correction. It is obvious that the grave significance of dyspepsia occurring after forty-five must be stressed persistently in undergraduate and postgraduate medical teaching, and that the public must also be made aware of this hazard.

* * *

Large numbers of patients with gastric cancer have lost their lives because their disease was confused with benign ulcer. A more aggressive approach to the problem of gastric ulcer should result in the salvage of many such patients.

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VAGINAL URETERAL ORIFICES*

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TRUE supernumerary kidney is a rare anomaly.[1] In a review of the literature Headings and Palmer[2] found a total of 44 cases, of which 6 had extravesical ureteral orifices. A case reported by Shane[3] and the following case bring the total number of cases of supernumerary kidney with a vaginal orifice to 8.

A. G., a 7-year-old girl, was seen because of urinary incontinence, which had been present since birth but was apparent only when the child was on her feet. There had been no nocturnal enuresis since the age of 2. With the patient in the supine position there was no evidence of urinary leakage, but examination when she was standing revealed an intermittent spurting of urine from what appeared to be a ureteral orifice in the vestibule of the vagina. Intravenous urography (Fig. 1) showed a supernumerary kidney on the left, located above a normal-functioning left kidney. A ureteral catheter introduced into the vaginal orifice ascended to the pelvis of the upper left kidney. Ureteronephrectomy disclosed a true case of supernumerary kidney. Convalescence was uneventful and was not followed by urinary leakage since. It should be pointed out that this child had been examined by several physicians, but always in the supine position, and that the family had been continuously reassured that she would outgrow this disability.

In 1937 Eisendrath and Rolnick[4] found in the literature 88 cases in which the ureter opened in the vaginal vestibule and 55 cases with opening into the vault of the vagina or the uterus. Since then, 6 cases[5–7] have been reported, bringing the total to 61.

D. C., a 35-year-old housewife, was admitted to the hospital complaining of lifelong incontinence of urine. The amount, although not excessive, was sufficient to require the wearing of a vulva pad at all times. The patient had been married for 7 years but had no children, a finding that is not unusual in cases of vaginal urinary leakage.

Physical examination was negative, except for urinary leakage from the vault of the vagina (not from the urethra).

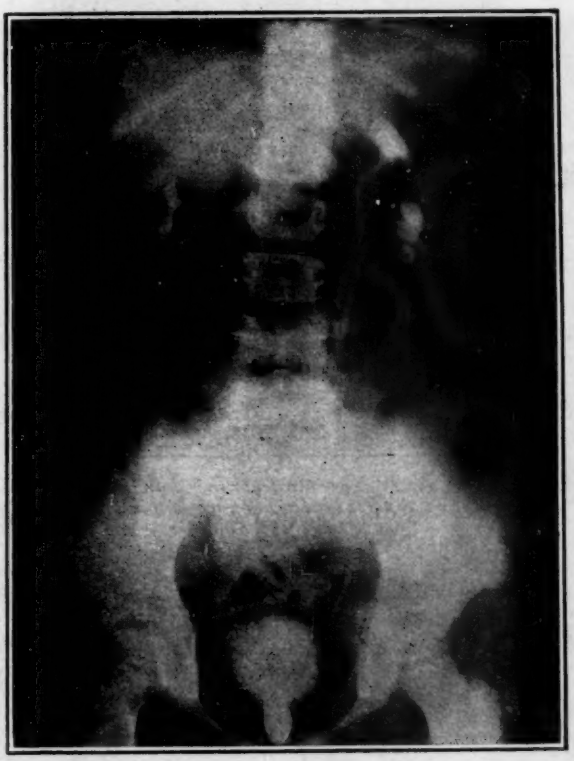

FIGURE 1. *Case 1. The intravenous urogram shows a supernumerary left kidney with a vaginal ureteral orifice.*

Laboratory study revealed normal findings. Intravenous urograms (Fig. 2) showed a normal right kidney, but no

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function was apparent on the left side. The left lateral wall and dome of the bladder were deformed by extrinsic pressure. A pelvic left kidney was immediately suspected. Gynecologic examination revealed a moderate-sized fibroid uterus, but no mass could be identified as kidney. The ureteral opening in the vagina was found deep in the vault and on the anterior wall. With much difficulty a No. 5 Fr. ureteral catheter could be passed about 1.5 cm. Skiodan was injected and ascended to about the level of the bladder deformity (Fig. 3). This seemed to confirm the tentative diagnosis of pelvic kidney, and a low-left-rectus incision was accordingly made, the left ureter being easily picked up. Dissection was carried down to the vagina and up as far as possible with this type of incision; no kidney was encountered. The peritoneal cavity was opened to permit better palpation of the abdomen. The right kidney was normal, but the left kidney fossa was empty. The bladder deformity was found to be due to the fibroid uterus. A diagnosis of aplastic left kidney was made, and about 8 cm. of the distal ureter was removed after double ligation with black silk. The proximal end was transplanted through the rectus fascia, so that if hydronephrosis developed, the ureter could be readily picked up and catheterized, and the location and character of the kidney determined prior to nephrectomy. This was never necessary. Six months after operation the patient was well, and for the first time since birth there was no urinary leakage.

FIGURE 2. *Case 2. The intravenous urogram shows a normal right kidney, no apparent function on the left and deformity of the left side of the bladder.*

In the cases reported above, careful attention to the case history and scrupulous inspection were sufficient to lead to the correct diagnosis.

FIGURE 3. *Case 2. This film shows the left ureter following the injection of skiodan into the vaginal ureteral orifice.*

SUMMARY

One case of supernumerary kidney with a vaginal ureteral orifice is described, and one of an anomalous ureteral opening in the vaginal vault, making the total numbers of such cases reported 8 and 61, respectively.

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THE USE OF STREPTOMYCIN IN COLON-BACILLUS PERITONITIS*

Report of a Case

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BOSTON

THE recorded clinical experience with streptomycin is as yet quite meager. The technic of administering this drug and the dosage to be employed in infections with various bacteria have not yet been established. The variation in susceptibility of different strains of the same bacteria and the rapid development of fastness in experiments in vitro suggest that a clinical evaluation of these factors is desirable.[1–3] The pooling of clinical experience with streptomycin in carefully studied cases therefore seems to be worthwhile. It is with this purpose in mind that the following report is presented.

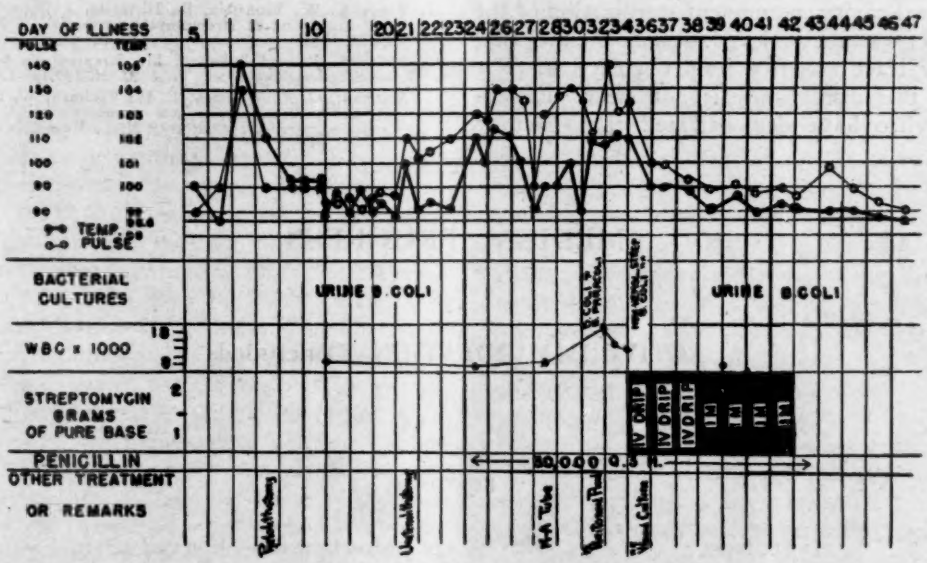

FIGURE 1. *Clinical Course.*

Note the effect of streptomycin on the temperature, pulse and white-cell count.

Case Report

W. S. (BIH 67286), a 50-year-old man, was admitted to the hospital because of pain in the left flank of 3 months' duration, associated at its onset in July, 1945, with chills and fever. Urologic investigation revealed a stone in the lower calyx of the left kidney and another stone at the left ureterovesical junction. The urine from the left kidney and from the bladder was full of pus and contained *Escherichia coli* on smear and culture. The urine from the right kidney was sterile. An attempt was made to expedite the passage of the ureteral stone by dilatation of the ureter through cystoscopic means. Four days later, however, the patient had sharp left-flank pain, chills and high fever, which proved to be due to the sudden passage of the stone from the calyx into the upper fifth of the ureter, the infection being thus bottled up in the left kidney. An immediate ureterolithotomy was done. At operation the retroperitoneal tissues were edematous, and the ureter was swollen. The ureter was incised over the stone, and after the stone was extracted, thick green pus, which contained *Esch. coli* on culture, drained from the kidney. Following this operation the patient made an uneventful recovery.

It then became necessary to remove the stone at the ureterovesical junction, to prevent the establishment of a permanent ureteral fistula as a result of the previous ureterolithotomy. Consequently, 12 days later, the lower left ureter was exposed through a Gibson incision. In this region the retroperitoneal tissues were also edematous. The peritoneum itself, however, was extremely thin. Despite gentle retraction 2 small holes were inadvertently made in the peritoneum. These were at once closed by suture. The ureter was then incised, the stone was extracted, and the wound was closed around a drain.

The postoperative course was stormy. The patient developed unmistakable signs of peritonitis with paralytic ileus — a rather infrequent complication after this type of surgery. A peritoneal tap revealed cloudy fluid containing pus and *Esch. coli* on smear and culture. Despite intubation of the small bowel by a Miller–Abbott tube, adequate chemotherapy with penicillin and sulfonamides, parenteral fluids

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The streptomycin used in this case was supplied through the courtesy of Dr. Gladys L. Hobby, of the Charles Pfizer Company, Brooklyn, New York.

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and transfusions of blood, the clinical status became progressively worse. The patient remained distended, toxic and irrational. On the 15th postoperative day, when the patient's condition was most desperate, streptomycin was obtained; during the first 3 days 2,000,000 units were administered daily by constant intravenous drip, and the patient was given 500,000 units intramuscularly every 6 hours for 4 more days.

The effect of this therapy was most dramatic (Fig. 1). The temperature and pulse rate dropped at once, and the patient became rational. The abdominal distention receded, and the patient took nourishment and passed normal stools. The peritonitis seemed to have been completely eliminated by streptomycin. The urine, on the other hand, became sterile and free from pus for only 2 days after the initiation of the streptomycin therapy. Thereafter, despite the daily administration of 2,000,000 units of this drug for a total of 7 days, pus and *Esch. coli* continued to be present in the urinary sediment.

A few points in this case history are worthy of comment. The patient was rapidly failing because of a severe colon-bacillus peritonitis, which was uninfluenced by any of the sulfonamides. A fatal outcome was unquestionably prevented by the use of streptomycin. It is interesting that although the bacilli were apparently completely eliminated from the peritoneal cavity, permanent sterilization of the urinary tract was not achieved, despite the fact that the urinary tract was free from obstruction. The reason for this discrepancy is not clear. Experiments in vitro have demonstrated that bacteria rapidly develop fastness to streptomycin.[2] The bacilli in the urine in the case reported above — but not those in the peritoneal cavity — apparently developed such a resistance. Whether the bactericidal effect of the streptomycin is affected by the character of the medium in which it acts (peritoneal exudate as against urine) or whether the peritoneum wards off infection more readily than the urinary tract remains problematical. The rapid development of bacterial resistance against streptomycin and the great variability in its bactericidal action against various strains of the same organisms[1] suggest that large initial doses are advisable for effective and permanent sterilization.

Summary

A case of colon-bacillus peritonitis that was successfully treated with streptomycin is reported, and certain pertinent points are discussed.

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MEDICAL PROGRESS

ACTIVE IMMUNIZATION (Concluded)

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Influenza

Following the identification of a virus agent causing human influenza,[314] efforts were made to develop vaccines effective in preventing or at least mitigating the infection. The finding of Burnet[315] that the fertile hen's egg provided a favorable medium for cultivating the influenza virus led ultimately to the use of this agent as the preferred culture medium. The demonstration that at least two distinct types of virus — designated "A" and "B" — could cause influenza[316,317] posed the necessity of producing an effective bivalent vaccine. Numerous studies, usually with monovalent preparations, gave more or less equivocal results, whether the vaccine was administered subcutaneously[318–320] or by inhalation.[321,322] There were occasional exceptions, as in the study by Henle et al.[323] in which a striking degree of protection was observed against influenza experimentally induced with a freshly isolated strain. A major improvement resulted from the discovery that the influenza virus could be efficiently concentrated by application[324] of the chicken-cell-agglutination phenomenon observed by Hirst[325] and McClelland and Hare,[326] the preparation of virus suspensions of greatly increased immunizing potency being made possible. It had already been noted on occasion that vaccines of higher than average virus content appeared to give more promising results.[320] Most of the succeeding studies, employing concentrated virus preparations,[327–331] produced higher immunity levels than had previously been attained, judged both by postvaccinal antibody titers and by resistance to natural or experimental infection.

Extensive confirmation of the value of a vaccine of this type was obtained in the study set up in 1943 under the Commission on Influenza, Army

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Epidemiological Board.[332] Over 6000 ASTP students in widely scattered parts of the United States received one dose of 1.0 cc. of a bivalent anti-A and anti-B vaccine prepared by concentration of the virus in infected chorioallantoic fluid, inactivated with formalin. An equal number of subjects served as controls. Influenza A in epidemic form appeared in each group at varying intervals, from twelve days before to five and a half weeks after vaccination was undertaken. Taken as a whole, the observed incidence of influenza among the inoculated was only 31 per cent of that in the controls (morbidity rates of 2.22 as against 7.11 per cent). The ratio of cases in inoculated subjects and controls varied greatly in individual groups, however, from a high of 1:6.0 (1.15 vs. 6.93 per cent morbidity) to a low of 1:1.5 (5.25 vs. 7.88 per cent). Best results were obtained when exposure to infection occurred a few weeks after vaccination, and at least a week's interval was necessary before any protection was evident. The poorest results were observed in the group experiencing the longest interval between vaccination and exposure to infection, but it is not entirely clear whether the relative failure in this group was due to the long interval or to other factors. Detailed reports of these studies present evidence that a multitude of factors determine the results to be expected following vaccination.[333–339] The conclusions to be drawn appear to be that immunization, with the vaccine employed, afforded a better than a three to one chance of protection, for a period of a few months, against the two most prevalent strains of influenza. A subsequent study, employing the same vaccine, indicated that protection may persist for as much as a year.[340] Furthermore, in this study and another more recently reported,[341] the incidence of influenza among vaccinated subjects was from one fifth[340] to one tenth[341] that in the controls. If these results can be confirmed, there will be a far more satisfactory basis for justifying the clinical use of the vaccine than has heretofore existed. Mass vaccination in the armed forces was wholly justifiable not only for the protection of large bodies of redeploying troops but also as a means of controlling what would have been an unparalleled opportunity for rapid and extensive spread of the disease if an epidemic had arisen. At present there is no apparent justification for widespread or routine use of the vaccine, in the absence of a clearly defined epidemic of influenza A or B. When a definite risk of exposure to either type of influenza exists, however, the vaccine may be used to protect persons whose circumstances warrant a special effort to prevent sudden illness, such as during the conduct of important personal or professional affairs and during travel. If the vaccine proves effective for as long as a year, its use on a large scale in the civilian population may deserve consideration — in the autumn of years that seem to be scheduled for one of the periodic outbreaks characteristic of influenza in its present form. The recent experimental infection studies of Henle et al.[342] throw an interesting light on the possible results to be expected from periodic reimmunization with influenza, suggesting that primary and accelerated reactions, analogous to the different vaccination reactions associated with varying degrees of resistance to smallpox, may be observed.

The essentially localized nature of the lesions of influenza has led to some skepticism regarding the results that may be expected from any parenteral route of immunization. It is on this basis that various investigators have attempted to immunize by inhalation of modified virus.[321–323] Burnet et al.[343] and Francis[344] have shown that a factor in nasal secretions is capable of inactivating influenza virus, and it has been demonstrated that this mechanism is enhanced by parenteral immunization.[345] It is fair to assume, therefore, that the production of an effective local resistance will be related to the production of a sufficiently high systemic level of immunity, but the surprisingly frequent finding of clinical influenza in persons exhibiting high antibody titers against the infecting virus has not yet been explained.

Local and constitutional reactions following administration of influenza vaccine have been widely observed, and are reported as occurring in from less than 1[334] to 59 per cent[339] of different groups. These extreme differences apparently depend both on the definition of a reaction and on the pains taken to obtain reports. Constitutional reactions have been sufficiently frequent and severe, at all events, to indicate the need for modifications in either the product or the dosage schedule, or both. The possibility that divided doses increase the efficacy of the vaccine has been suggested by animal experiments,[346] and would be expected on a theoretical basis. Antibody titrations on human subjects, however, have not borne this assumption out.[327, 347] In fact, Hare[348] has suggested that secondary antibody responses from repeated doses of influenza vaccine are not to be expected, since the first injection is in all probability actually a booster dose for the great majority of subjects.

Several considerations warrant a conservative attitude toward the use of influenza vaccine, even if improvements in the vaccine should lead to a higher degree of protection over longer periods. Foremost among these is the possibility that sensitivity to the egg proteins in the vaccine will induce severe reactions. Among the 6000 ASTP students inoculated in the study referred to above, an asthmatic reaction occurred in only 1 case[336] and an urticarial reaction in 1.[338] At least one fatal reaction has been observed, however, following the use of a vaccine prepared from hen's eggs,[349] and such reactions may be anticipated more frequently in persons receiving repeated booster injections of a vac-

cine of relatively short-lived effectiveness. It is to be hoped that from the experience of the armed forces a sufficient evaluation of allergic reactions to egg vaccines will have accumulated to determine at least tentatively the significance of such reactions. The possibility of employing eggs from ducks or turkeys, as suggested by Berkowitz[350] for typhus vaccine, should be further explored.

Numerous modifications of the liquid concentrated allantoic fluid vaccine have been tried. Precipitation with alum[351] or protamine[347] did not appear to enhance the potency materially, whereas a vaccine suspended in oil[347, 352] by Freund's method[353] induced a rather high incidence of untoward local reactions. Salk[354] has recently applied a technic long employed in potentiating antigens used in animal immunization, by adsorbing the vaccine virus on calcium phosphate, with preliminary results that appear promising. Such measures may prove particularly satisfactory when combined with improved methods of concentrating and purifying the virus. The differential centrifugation developed by Stanley[355] appears to be highly effective, and further information on the alcohol-concentration method of Tovarnizky[356] is awaited with interest. Improved means of inactivating the vaccine with minimal injury to its antigenic potency, such as the use of ultraviolet irradiation,[346, 355] may further enhance the efficacy of the vaccine.

All the advances outlined above merely serve to increase the immunizing potency of the currently available egg-adapted strains of influenza virus. Burnet[357] showed that egg adaptation is accompanied by fundamental changes in the biologic properties of the virus, and a far larger body of evidence than is now available will be required to determine whether such a modified antigen can retain its clinical effectiveness as well as the vaccinial modification of smallpox virus. Evidence already indicates that the influenza virus strains in current use for preparation of vaccines are antigenically somewhat apart from those isolated in recent epidemics.[336, 338] Likewise, apparent antigenic differences between prevalent epidemic strains have been demonstrated.[359, 359] The observations of Beveridge and Burnet,[360] Shope[361] and others, however, suggest that, by selection of appropriate strains or by repeated vaccination, immunity of a broader antigenic pattern than that induced by single injections of the currently available vaccines is possible. It is well to bear in mind that the exact etiology of the influenza pandemic of 1918 is still unknown and, in all probability, will never be determined. No one can predict with assurance — although Shope[361] has made a brilliant approach to this problem — what the biogenesis of the next epidemic will be, and one is left to ponder the following still appropriate editorial comment[362] of three years ago:

> Spectacular as have been the advances in recent years in research in influenza, it cannot be said that, faced with a disaster such as that of 1918, we are yet in a position to do anything very dramatic in order to prevent its spread. The virus responsible for the next pandemic will almost certainly be one that is unrelated to those now isolated. For this reason it will be necessary first to isolate the virus. This in itself may be a difficult proceeding, for a susceptible animal will first have to be found. Even supposing this proved to be possible, the manufacture of vaccine in sufficient time for use in the epidemic is — by all present indications — a sheer impossibility. And vaccines compounded from known strains will almost certainly be useless.

Smallpox

The continuing importance of maintaining adequate smallpox immunity, wherever one may be, is attested by reports such as that of the Hongkong epidemic of 1937–1938, in which 2000 persons died,[363] of the Glasgow outbreak of 1942, which, although nipped in the bud, killed 24 per cent of those infected,[364] of 5 deaths among 23 cases in American troops in the China-Burma-India Theater[365] and of the recent outbreak of virulent smallpox in Seattle, imported by American troops returning from the Orient. One still occasionally hears the claim that the reduction in smallpox, where it has been achieved, is the result of improved sanitation. Rogers[366] has outlined the fallacy of this argument so far as India is concerned, where decreases in smallpox morbidity are observed side by side with an unchanged prevalence of such diseases as cholera. Nor is it pertinent to claim that present-day smallpox is mild and therefore unimportant, for it is well established that the mild and severe forms may alternate in successive epidemics or coexist in the same one. Finally, the relation between the incidence of smallpox and the extent and effectiveness of vaccination laws has been so conclusively shown[367, 368] that space will not be taken here to repeat the evidence.

The shifting populations of the recent war years have provided a fertile soil for transmission of smallpox and have put current vaccination programs and methods to a rigorous test. Although several incipient epidemics of smallpox resulting from these conditions were readily checked by vaccination, the small number of failures reported may serve as a basis for critical consideration of the requirements that must be met to achieve successful vaccination. In any such consideration it must again be emphasized that no immunization procedure is absolutely effective. The causes of vaccination failures can nevertheless for the most part be itemized, as follows:

Long interval since vaccination. The occurrence of smallpox in persons not vaccinated for many years merely points by contrast to the effectiveness of vaccination in persons also exposed who, having been vaccinated more recently, are found to be clearly protected.[369]

Use of impotent vaccine. Smallpox vaccine is a living virus when properly prepared, and successful vaccination depends on the ability of this virus to multiply in the tissue of the vaccinated person. Multiplication of the virus in the host may fail for many reasons, including the following: improperly prepared vaccines (only by the practice of unceasing vigilance, even in a properly equipped and operated laboratory, is it possible to distribute a vaccine of consistently adequate potency; the operation of numerous small and inadequate vaccine establishments scattered through the Orient offers a possible explanation of the relatively frequent failure of vaccination seen in that part of the world[370]); improper storage of vaccine (vaccine virus, if refrigerated, lies dormant and retains its potency, but if allowed to warm up, it rapidly exhausts the metabolic resources of its suspending medium and dies; thus, failures to produce a successful reaction may be due to carrying the vaccine in the pocket or keeping it on a drugstore shelf — to be dependable, vaccine virus must have been stored at temperatures below freezing for as much of the time as possible, and the colder the temperature the better, since it is impossible to injure the virus by any available degree of cold); use of outdated vaccine (because it is usually not possible to keep smallpox vaccine continuously below 0°C. at all times during shipping and handling, the vaccine necessarily undergoes some deterioration, and is therefore given a relatively short expiration date — for example, not over six weeks in Massachusetts — beyond which it cannot be regarded as dependable); and the use of less than the full contents of a capillary for each vaccination (this may result in failure, since on long standing the virus-laden lymph tends to separate from the clear glycerin portion, which is relatively inactive[372]).

Faulty vaccination technic. A fully potent virus may fail to multiply in the vaccinated subject, because of any one of various errors in technic. Thus, the presence of such antiseptics as alcohol, mercurochrome and iodine on the vaccination site destroys the virus as soon as it is applied, and failure to achieve the right degree of penetration of the skin prevents the virus from obtaining a suitable site for multiplication. In a recent study in which two physicians used the same virus at the same time, one obtained twenty successful reactions out of twenty vaccinations, whereas the other obtained only six out of seventeen, the only difference being that the less successful physician failed to break the skin surface consistently with the needle.[371]

Incorrect interpretation of the result obtained from vaccination. A definite vesicle appearing at the site of vaccination is unmistakable evidence of a successful primary or accelerated reaction, but the small papule characteristic of an immune reaction is less specific, and may be simulated by a traumatic reaction to the application of the needle. Furthermore, persons who have previously been vaccinated may exhibit a local allergic reaction to the antigenic substances in smallpox vaccine. A "dead" vaccine may thus induce a small papule, indistinguishable from an immune reaction except that it appears and disappears somewhat earlier.[373] It is significant that the patients in the 23 cases of smallpox in the China-Burma-India Theater mentioned above were each recorded as having shown an immune reaction following vaccination, and similar experiences have been reported in the British Army in the Middle East.[374] Indeed, Marsden[375] says that the immune reaction should on no account be regarded as a successful result, since it does not necessarily indicate immunity, although often shown by immune subjects, and that persons who give this reaction but have histories that are at all uncertain should be vaccinated again and again. Marsden, however, acknowledges the validity of interpreting a deep-seated indurated swelling, developing about the third day and subsiding gradually, as a reaction of immunity.

Concerning the closely related subject of the person who cannot be vaccinated, d'Arcy et al.[376] describe a hospital ship outbreak of 6 cases, in 5 of which the patients had recently been unsuccessfully vaccinated. Smith,[377] the health officer meeting the ship at its first port of call, notes that in the prompt control of the outbreak, several persons were successfully vaccinated whose vaccinations had never previously been effective. One suspects that Dr. Smith was vigorous with the needle; indeed, it has repeatedly been recommended, particularly by British writers,[378] that two or more insertions be employed whenever maximum protection against smallpox is urgent. Horgan and Haseeb[379] have demonstrated, by the use of duplicate sites on previously vaccinated persons, that not all revaccinations produce the same result even under identical conditions at the same time; in their subjects the percentage of successful reactions, and hence the apparent ratio of accelerated to immune reactions, varied with the character of the virus preparation used. Nagler[380] agrees with Horgan and Haseeb in recommending duplicate insertions on persons with a definite or probable history of previous vaccinations. It is worth noting at this point that a correlation between visible vaccination scars and resistance to smallpox in persons with histories of previous vaccination has been observed.[381] Some lay officials even require a visible vaccination scar as a basis for accepting a vaccination certificate.[382] This, of course, is unjustified, since vaccination by the multiple-pressure method usually leaves a scar that is subsequently difficult to find. The

responsibility must remain with the physician, to ensure that nothing less than a clear-cut immune reaction is observed before permitting a patient to risk exposure to smallpox.

Variations in the host-parasite relation. These can involve differences in vitality or specificity of the vaccinia virus employed, in the infectivity of the strain of smallpox encountered, and in individual response to the immunizing process. It is difficult to believe that 20 out of a group of 62 subjects exhibiting successful primary reactions could have manifested such reactions not more than fifteen months earlier, as reported by Minning,[383] unless there were a qualitative difference in the two strains of vaccinia virus used. Stevenson,[378] on the other hand, is inclined from analogy with animal studies to believe that the differences in protection observed following vaccination are due to differences in the immune response of the host. Evidence for such a concept is not readily adduced, but fairly convincing evidence has recently been presented that vaccinia virus strains of completely unrelated origin provide approximately equivalent protection against a virulent endemic strain of smallpox.[384] For practical purposes, it is therefore wise to follow the simple dictum of d'Arcy[376] that it is only the successful vaccination that counts, to persist in vaccinating until a successful vaccination is achieved, and to revaccinate at intervals of five to seven years and whenever vaccination is otherwise indicated.

Little can be said regarding the optimum age for vaccination, since few observations on this point have been made. Ratner[4] offers the reasonable statement that the ideal time for vaccination is between three and six months of age and cites data regarding neonatal vaccination, mostly confirming the general impression that successful reactions at this age are undependable. It is almost universally agreed, chiefly for reasons given below, that vaccination should be performed not later than the first year of life.

At present virtually all smallpox vaccine available is prepared by inoculation on calves, carabao, sheep or similar herbivora, but the virus can be successfully cultivated in tissue media[385] and the chorioallantoic membrane of the chick embryo.[386] Vaccines have been prepared by both methods. Results with tissue-culture vaccine (inoculated intradermally) have been poor, the immunity being apparently quite transitory,[387, 388] perhaps owing to an insufficient concentration of virus in the material employed. Chick-embryo vaccine has given promising results in the hands of several workers,[379, 380, 389] is being employed on a limited scale in this country and elsewhere, and is strongly favored in principle by some investigators. One study with egg vaccine in this country indicated that the material employed induced a substandard immunity and a deeper than average tissue reaction at the site of vaccination. Nagler[380] on the contrary, observed that the reaction induced is more superficial than that produced by calf vaccine, and that immunity depends largely on the virus content, regardless of the source of the virus. One may safely predict that chick-embryo vaccine will be used on a much larger scale in the future, unless allergic reactions to vaccines derived from hen's eggs[349] prove to be an obstacle.

Intracutaneous vaccination, as employed by Rivers and others[387, 388] has been tried in the hope that immunity could be achieved without the necessity of producing a cutaneous vesicle. Results with chick-embryo virus given by this route have been little better than those with tissue-culture material.[390] Even less promising were the results obtained with a formalinized vaccine.[391]

Combinations of smallpox vaccine with other immunizing agents are rare; Blanchard[392] has reported the use of a mixed yellow-fever and smallpox vaccine. Combined immunization with smallpox and typhoid vaccines is a curiosity that has been reported by a Japanese,[393] as one might almost expect — incidentally, the only modern report of peranal immunization for any purpose is also from Japan.[394]

Reactions, in a small percentage of persons vaccinated, continue to be reported from time to time. Autoinoculation on various body sites may occur in vaccinees,[395–397] and is also occasionally observed among workers in contact with smallpox vaccine at this laboratory and elsewhere.[398, 399] Thirty-four mild and miscellaneous skin eruptions were observed among two hundred and seventy-four thousand vaccinations in the Edinburgh outbreak.[395] Several types of rashes occur, varying from a local erythema of greater or less extent that is a constant accompaniment of successful vaccination to lesions that embrace either the affected arm or other parts of the body[400] and even to generalized vaccinia. Whether generalized vaccinia is to be distinguished from eczema vaccinatum is debatable; the excellent reviews of Jubb[401] and of McKhann and Ross[402] offer detailed discussions. The incidence of this complication is variously reported, but English and American figures[401–403] indicating that there is about 1 case in forty thousand vaccinations are representative. Since most cases appeared in eczematous patients and the mortality rate was disturbingly high prior to the advent of the chemotherapeutic drugs, it has been universally recommended that persons with eczema be protected from any contact with vaccinia virus, either direct or indirect, except when exposure to smallpox is likely. Treatment with convalescent serum has been employed[404] but is of extremely doubtful value in this as in all other virus diseases. Furthermore, the syndrome is not always due to the vaccine virus. Recent case reports demonstrate that Kaposi's so-called "varicelliform

eruption," which in turn is indistinguishable from eczema vaccinatum, can arise from infection with the virus of herpes simplex.[405–407] Thus eczema vaccinatum should be regarded as a syndrome arising basically from eczema rather than from vaccination. Hershey and Smith[408] point out the desirability of dropping the older clinical designations quoted above, specifying instead the virus and the underlying cutaneous disease, if any.

Although far rarer than generalized vaccinia, postvaccinal encephalitis is still observed occasionally in Europe and rarely in this country. Seven cases, 2 of which were fatal, were reported following some five hundred thousand vaccinations in the Edinburgh area in July, 1942.[409] In Fife, on the other hand, 9 cases were observed in seventy-three thousand vaccinations.[410] Thus the incidence continues to vary tremendously in different series; in this country it can scarcely be greater than 1 in two hundred thousand. In dealing with such a rare condition, when the diagnosis is at best made by inference and when several known and no doubt several other unknown etiologic agents may induce a virtually indistinguishable picture, it is difficult to arrive at any significant conclusions. Although cases in infants do occur,[411, 412] the incidence is probably not over 1 in eight million.[411] Moreover, encephalitis is extremely rare after revaccination.[411] Hence it could probably be rendered even rarer by primary vaccination in infancy, which is also to be preferred for many other reasons. Treatment with convalescent serum has been used[412, 413] but is subject to the limitations mentioned under generalized vaccinia.

Postvaccinal tetanus has virtually been eliminated since the role of vaccination dressings, bunion pads, contaminated bone points and other factors in the etiology of this complication has been publicized. Nevertheless, the disregard of such well founded precautions is still occasionally followed by tetanus.[414] Miscellaneous complications continue to be related to vaccination from time to time,[415–417] but without substantial evidence that the relation is more than coincidental.

Rabies

Any attempt to evaluate antirabic vaccination on the basis of available experimental or epidemiologic evidence is somewhat inconclusive, as shown in the extensive review by Webster[418] and compactly summarized recently by Casals.[419] The lack of extensive convincing evidence for the efficacy of rabies vaccine in preventing experimental animal infection was formidably exposed in Webster's thirteen-page table summarizing such experiments. Moreover, the epidemiologic data cited by Webster — derived chiefly from McKendrick[420] — certainly do not provide any conclusive proof that antirabic vaccination protects human beings from the disease. Nor is there any comfort in the finding of Denison and Dowling[421] in Alabama that rabies occurs with approximately equal frequency among Whites, who often seek antirabic treatment, and Negroes, who rarely apply for such treatment. Furthermore, these authors point out that among the 48 human deaths from rabies in the seventeen-year period considered, 23 occurred in persons judged to have received prompt and adequate treatment. They conclude that there is little relation between mortality from rabies and the administration of vaccine. On the other hand, the findings of Palik and Moss[422] that the mortality rate in treated persons was greater following bites from proved as against unproved rabid animals, from head bites as against bites elsewhere and in Negroes as against Whites, could be equally well explained by the assumption either that the vaccine gave only a partial protection or that it gave no protection whatsoever. Only their finding (confirmed by McKendrick's much larger series of cases) that delay beyond fourteen days in seeking treatment markedly increases the risk of death from rabies gives support to the belief that rabies vaccine is of value in human beings.

Such data, however, are by their very nature inconclusive. They may be influenced by a great variety of uncontrollable but highly important factors. First among these is the actual rarity of human rabies; 48 cases of any disease over a seventeen-year period,[421] for example, scarcely provide statistically significant data. Also, multitudinous factors influence the chances of infection: location of the bite, depth of the bite, entrance of saliva into the wound (as affected, for example, by clothing), local treatment applied, interval before seeking local or systemic treatment and so forth. Since such factors are always present in human exposure to rabies and since it will always be virtually impossible to obtain a properly controlled and statistically significant series of untreated cases, the evaluation of antirabic vaccination by epidemiologic methods must remain an unsatisfactory approach, and results based on this approach must be judged accordingly.

Regardless of statistical data, the experience of years has firmly established the belief, among all who have studied the problem, that antirabic vaccination greatly reduces the chances of contracting rabies. Webster,[418] after reviewing the lack of evidence for the efficacy of the vaccine, proceeds to furnish a detailed and elaborate schedule of the indications for vaccine treatment. And despite the fact that rabies is rare (no human case having occurred in Massachusetts, for example, since 1935), the disease is so horrifying to most minds and death from it is so absolutely certain that people continue to demand and physicians to administer the vaccine, with its attendant discomforts and risks, rather than face even a remote prospect of succumbing to rabies. It has little practical bearing on the case that most people think nothing of daily

risking death (or, what is sometimes worse, survival) from spinal-cord injury or skull fracture following an automobile accident. Rabies remains a fear-inspiring menace in the mind of man, and will continue to do so whenever the possibility of contracting the disease exists.

Many of the inconclusive results reported following antirabic treatment were undoubtedly due to the use of ineffective vaccines. It is only within the last few years, beginning with Webster's development of a mouse test for measuring the immunizing potency of rabies vaccine,[422] that evaluation of such vaccines and directed efforts toward their improvement have become practical. This method, which was found by others to provide a valid basis for distinguishing between potent and impotent batches of vaccine,[424] was further developed by Habel[425–427] and is included in the minimum requirements for rabies vaccine established recently by the National Institute of Health.[428] Concurrently, various studies have been in progress on the improvement of rabies vaccines. Hodes et al.[429] showed that an effective vaccine could be obtained from rabies-infected tissue inactivated by ultraviolet irradiation, and an improvement on this principle has been developed by Levinson et al.[273] Meanwhile, Webster and Casals[430] had made the not unexpected finding that the potency of a rabies-vaccine preparation depended to a large extent on its virus content. This finding has been confirmed,[427, 431, 432] and probably explains the relatively high efficacy of Kelser's chloroform-killed dog vaccine,[433] which contains a much larger amount (33 per cent) of brain and cord tissue than is ordinarily used. Furthermore, several investigators have found differences in the effective or immunizing properties of various strains of fixed virus[426, 434] suggesting the importance of proper selection of strains for vaccine production. Hence, the prospects are that the quality of rabies vaccines available hereafter will be both superior to and more consistent than that of the vaccines of the last fifty years.

Further evidence of protection against rabies has been forthcoming in experimental and field use of the vaccine in dogs. A few years ago it was authoritatively stated that "as yet there is no authentic or convincing evidence that would lead to the belief that successful antirabic vaccination for dogs is available."[435] However, Leach and Johnson,[431, 436] Damon[432] and others demonstrated that a good vaccine provides excellent protection against experimental infection, that a poor grade of vaccine provides only moderate protection and that unvaccinated control animals have a significantly greater fatality rate than the vaccinated groups. Furthermore, the field results are impressive. Beginning in 1937, over 6000 dogs a year have been vaccinated in Montgomery County, Alabama, simultaneously with a much less extensive program for disposal of stray dogs. The animal rabies incidences in this county from 1936 to 1943, respectively, were 74, 23, 29, 0, 1, 0, 0 and 1. On the other hand, Mobile County, where dog vaccination was opposed, exhibited a continuously high incidence of animal rabies throughout this period.[437] Experience in Massachusetts has been similar, although less extensive. Because the state laws make effective dog quarantine virtually impossible, a dog-vaccination campaign was begun in 1934 and stressed particularly in communities in or near areas reporting animal rabies. Either because of these inoculations or because of the natural rhythm in the rise and fall of the disease, cases of rabies in animals have declined since 1934, as indicated by the following figures[438]:

YEAR	NO. OF CASES	YEAR	NO. OF CASES
1930	310	1938	58
1931	304	1939	39
1932	131	1940	73
1933	171	1941	31
1934	331	1942	20
1935	278	1943	5
1936	136	1944	1
1937	211	1945	0

Dog vaccination, therefore, appears to furnish a promising means of controlling the principal reservoir of the disease. Occasionally, when rabies becomes seeded in wild animals,[439, 440] vigorous, specific eradication measures are highly effective in clearing up such foci. By and large, however, in a country such as the United States, where the disease cannot be kept out as in Australia and Hawaii, or eradicated as in England and Scandinavia, the best available measure for its suppression lies in building up the resistance of the dog population. Vaccination clearly does not provide a dog with absolute protection, but it does appear to increase the resistance sufficiently so that the minimal infective dose of virus is increased, and hence only the deeper bites, or those with an exceptionally high virus content, manage to infect. It has been pointed out by Anderson[441] for rabies, and by many others for diphtheria and other diseases, that if the frequency of transmission of a disease is reduced below a certain level, the disease tends to die out of itself. This is the rationale of continuing and extending the program of antirabies dog vaccination recommended by the Massachusetts Department of Public Health. Such a program must, for obvious reasons, go hand in hand with the elimination of stray dogs; some of the attendant problems of dog control and the ways in which they may be successfully surmounted have recently been pointed out by Hewitt.[442]

The decision whether to administer rabies vaccine depends on a number of factors, and there are many different recommendations regarding the exact rules to follow. It is universally recommended that the wound be cauterized with nitric acid. Shaughnessy and Zichis,[443] however, questioned the

evidence on which this procedure is based and showed that, in experimentally infected guinea pigs, irrigation with a 20 per cent solution of soft soap is as effective as chemical cauterization with fuming nitric acid — and possibly even more effective. The administration of rabies vaccine is usually carried out in one of the following situations: a definite bite by a proved rabid animal; a definite bite by an animal in which rabies cannot be excluded — either the animal was lost track of or pathological examination was inconclusive; and any definite bite on the head or neck — treatment should be given while the animal is being observed and suspended if the animal is well seven days after the bite.

No general agreement exists regarding the possible channels of infection, besides definite skin-penetrating bites, that require treatment. Such situations may vary so widely that they are not subject to generalizations but must be considered individually.

Reactions to rabies vaccine have been reviewed by McKendrick[420] and summarized by Webster[418] and Casals.[419] In slightly over a milllion treatments, major paralytic accidents occurred in 181 subjects (1 in 5861), and 48 were fatal (1 in 22,100). Neurologic complications were more frequent following the use of attenuated virus vaccines than with vaccines prepared from killed virus (1 in 3398 as against 1 in 8887). This supports the theory that such reactions are due to traces of viable and infective fixed virus. Kelser[444] suggests that their occurrence with the use of phenolized (Semple) vaccine may be explained by the ability of phenol to coagulate proteins, so that occasional units of viable virus are left within a coagulated particle. Whatever the explanation, the occasional occurrence of these complications is sufficient contraindication to the administration of antirabic treatment unless there are clear-cut indications for its use.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 32361

PRESENTATION OF CASE

A sixty-year-old housewife entered the hospital because of hematuria.

The patient was apparently well until three months before entry, when she fell, fracturing the left wrist. Following this accident she had a bout of painless hematuria, with the passage of small dark clots two or three times a day for three days. There was no concurrent frequency, urgency or other urinary symptoms. She remained asymptomatic until twenty-four hours before entry, when she suddenly passed bright-red blood while straining to urinate. During the night she urinated at hourly intervals, with some dysuria and difficulty in starting the stream. There was no incontinence, costovertebral-angle pain, chills or fever. She had had no previous urinary symptoms, and there was no recent weight loss, change in bowel habits or melena.

Twenty years before entry the patient had a tumor "filled with water" removed from the right lower quadrant of the abdomen. Seven years before entry, following a period of weakness, weight loss and slight postmenopausal bleeding, a hysterectomy was performed at a local hospital. She was not called back for a follow-up and received no x-ray treatment. She had had no vaginal bleeding since this operation. The menopause occurred fifteen to twenty years before entry.

On physical examination the heart and lungs were negative. There was slight tenderness in the suprapubic region. Pelvic examination revealed a second-degree perineal laceration and slight tenderness in the region of the bladder.

The temperature, pulse, and respirations were normal. The blood pressure was 160 systolic, 90 diastolic.

Examination of the blood showed a red-cell count of 5,050,000, with 90 per cent hemoglobin, and a white-cell count of 19,700, with 88 per cent neutrophils. The nonprotein nitrogen was 35 mg., and the total protein 6.5 gm. per 100 cc. The chloride was 98 milliequiv. per liter, and the carbon dioxide 26.9 milliequiv. The urine was grossly bloody and gave a ++++ test for albumin.

Cystoscopy showed dark-red blood oozing from the right ureteral orifice. Clear urine was discharged from the left ureter. On the posterior wall of the bladder, in the midline and extending up to the dome and to the right, was a red, thickened area of mucosa covered by a layer of whitish slough or fibrin. A 3-mm. papillary mass was seen in the center of this area. Several biopsy specimens from this lesion were reported as showing acute and chronic inflammation.

An intravenous pyelogram showed no excretion of dye on the right side over a period of sixty minutes. The left kidney was small and excreted the dye promptly. The bladder contained lobulated filling defects having the appearance of blood clots. There were multiple small calcifications in the spleen. A retrograde pyelogram showed obstruction of the right ureter 6 cm. above the ureteral vesical junction, where there was a caplike defect in the upper margin of the dye (Fig. 1). A plain film of the abdomen showed a large soft-tissue mass in the pelvis that reached to the level of the fourth lumbar vertebra and was consistent with a distended bladder; there were several dilated loops of small bowel. An x-ray film of the chest showed a considerable amount of fibrosis throughout both lung fields and two rounded areas of increased density in the left lung field.

The patient had several episodes of acute urinary retention and intestinal distention. An operation was performed on the eleventh hospital day.

DIFFERENTIAL DIAGNOSIS

DR. J. DELLINGER BARNEY: The fact that this patient had an episode of painless hematuria lasting for two or three days following a relatively minor fall may mean either that the fall was not so insignificant or that it lighted up some quiescent lesion in the kidneys or bladder. The absence of accompanying frequency, urgency or other symptoms tends to eliminate an inflammatory process. On the other hand the return of the hematuria some twenty-four hours after the initial episode, this being accompanied by considerable frequency, with dysuria and difficulty in starting the stream, suggests some inflammatory process arising subsequent to the injury. The absence of costovertebral-angle pain, chills and fever seems to rule out, or at least to decrease, the possibility of definite kidney infection.

Going on to the next item, the tumor "filled with water," which the patient said was removed twenty years before entry, may have been an ovarian cyst or something malignant, although the length of time that had elapsed since the operation rather tends to remove the latter possibility. The history of a hysterectomy seven years before entry for vaginal bleeding associated with symptoms of loss

of weight and weakness suggests malignant disease of the uterus, but the patient might have had fibroids.

The white-cell count of the blood was considerably elevated, with a rather abnormal number of polymorphonuclears. The bloody urine was consistent with the history, and it is unfortunate that nothing more than blood and albumin was reported. One would like to know whether there were pus cells or bacteria. The fact that cystoscopy showed dark blood coming from the right ureteral orifice seems to limit the source of bleeding to the right kidney or ureter. Also, the clear urine coming from the left kidney, together with the x-ray appearances of a normal kidney on the left side, appears to eliminate the left kidney as a source of the hematuria. The conditions described on the posterior wall of the bladder strongly suggest a sloughing and infiltrating neoplasm, which was either primary or an extension from some other source. I say this in spite of the fact that several biopsy specimens showed only acute and chronic inflammation. It is possible that, together with the inflammatory tissue, there was neoplastic tissue. The statement that the intravenous pyelogram showed no dye on the right side in a period of sixty minutes indicates that the kidney was either entirely absent or was badly diseased. The lobular filling defect in the bladder, which was thought to suggest blood clots, is interesting but does not necessarily contribute anything more than the cystoscopic findings. The lesions seen in the bladder and shown by x-ray may, in fact, have been organized adherent blood clots, but the possibility of neoplasm or inflam-

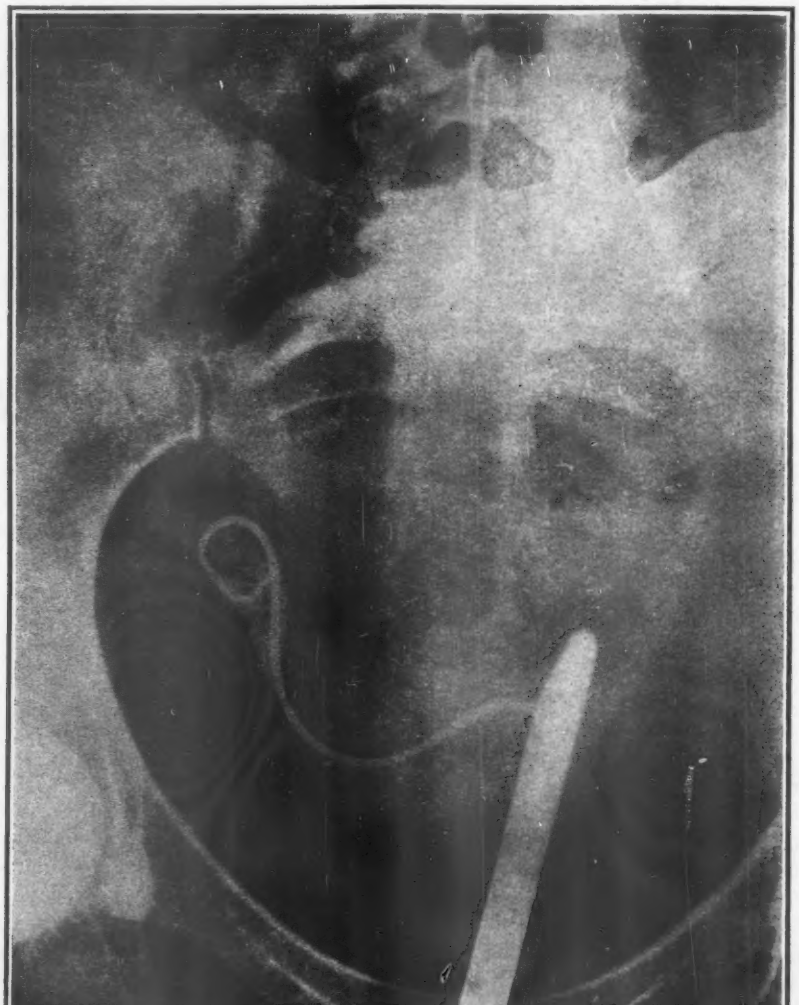

FIGURE 1.

matory tissue cannot be avoided. I do not believe that the calcification seen in the spleen is of any particular significance.

The important observation, however, was that in trying to do a retrograde pyelogram definite obstruction in the right ureter at a level of 6 cm. above the ureteral orifice was found. May I see the films?

DR. MILFORD D. SCHULZ: The films show nonvisualization of the right kidney because of an obstruction in the lower portion of the right ureter, which is shown on attempted retrograde filling. The catheter apparently would not pass beyond the lowermost 6 cm. of the ureter, where an irregular filling defect is lined by opaque material injected through the retrograde catheter. This has the appearance of a ragged non-opaque defect, possibly a polypoid soft-tissue mass, blood clot or stone. The soft-tissue mass seen arising from the pelvis on one film seems to be a distended bladder. Many defects in the visualized bladder are transient and are probably blood clots. The areas of density mentioned in the chest films may be metastases, but they are not too impressive.

DR. BARNEY: The record does not state whether any urine was obtained from the right kidney. The so-called "cap-like defect" in the dye that was injected into the right ureter may have been due to a variety of things. It may have been caused by a simple stricture, which was associated with more or less dilatation of the ureter. It may have been due to stone, which was either non-opaque or slightly so. It may have been caused by a neoplastic growth.

The films of the abdomen, which are said to show a large soft-tissue mass, may have indicated a neoplastic growth with adherent loops of small bowel or a full bladder. I am not able to interpret the various areas of density seen in the twenty-minute film of the bladder, especially the two or three that are just to the left of the midline. These may represent areas of calcification, either within the bladder or outside it. On the other hand they may be small collections of dye in the saccules or folds of the lesion seen by cystoscopy. I do not believe, however, that these areas of density represent calcification. The films of the chest show fibrosis, and the two round areas of increased density in the left lung field may represent either tuberculosis or metastatic cancer.

I am not able to throw much light on the episodes of acute urinary retention and intestinal distention that occurred before operation. Again, however, all this may have been due to the fact that there was malignant disease outside the bladder in the pelvis, with adhesions between loops of small bowel and with a splinting, one might say, of the bladder so that it could not empty itself in the normal manner.

In looking over all these facts about the case I think one can say that the initial episode of hematuria originated in a lesion already existing in the bladder before the fall that the patient sustained. The onset of urinary symptoms, such as the dysuria and the difficulty in starting the stream, together with the nocturia, suggests a rather long-standing process in the bladder. I think that a kidney lesion can be ruled out, owing to the absence of the usual kidney symptoms, such as pain and tenderness. The fact that there was no recent weight loss or change of bowel habits does not necessarily rule out cancer. I do not believe that the abdominal tumor removed twenty years before entry had anything to do with the present situation. I do, however, think that the hysterectomy, together with the history of weakness, loss of weight and vaginal bleeding, is suggestive of cancer of the uterus. The cystoscopic find-

FIGURE 2.

ings indicate a lesion rather low down in the right ureter, and in the absence of stone or any evidence of a simple stricture, I think that this patient had a carcinoma of the ureter on the right side, probably metastatic from carcinoma of the uterus, with extension into the bladder. This may have accounted for the soft-tissue mass in the pelvis that was reported by the radiologist, but I confess that this finding does not impress me too much.

Clinical Diagnosis

Carcinoma of ureter.

Dr. Barney's Diagnosis

Carcinoma of ureter, right, with extension into bladder (? metastatic from uterus).

Anatomical Diagnosis

Papillary carcinoma of ureter, right.

Pathological Discussion

Dr. Benjamin Castleman: The operation consisted of a right ureteronephrectomy. The ureteral obstruction, which had produced a moderate hydroureter and hydronephrosis, proved to be a grayish-yellow friable obviously carcinomatous mass 4 cm. in length involving the entire circumference of the ureter and apparently completely occluding its lumen (Fig. 2). The wall was invaded, but the serosa was perfectly smooth. Microscopically it was a papillary carcinoma of the transitional type of epithelium that normally lines the ureter and bladder. There was no extrinsic tumor, and no involvement of the bladder. The defects seen in the bladder were almost certainly blood clots, because when the patient was last seen two months postoperatively, the bladder looked perfectly normal.

Papillary tumors of the renal pelvis and ureter have been known to implant in the bladder, although there still is some question whether the bladder lesions are implants or autonymous growths. Personally I am inclined to favor the latter thesis.

CASE 32362

Presentation of Case

A forty-three-year-old housewife entered the hospital complaining of pain in the right lower quadrant of the abdomen.

The patient had had ulcerative colitis for about twelve years, with many remissions and exacerbations. The last episode of active colitis took place seven months before admission, when she was hospitalized for three weeks for study and treatment. After discharge she remained well until a month before admission. Coincident with the onset of the menstrual period there was an ache in the right lower quadrant, with nausea and vomiting that lasted three days. The ache disappeared when the period ceased, and the patient was well until six days before admission, when the next period started. Five days before admission she noticed in the right lower quadrant a slight ache that within twenty-four hours developed into a severe pain, radiating around the right flank and up toward the right costal margin. She was nauseated, vomited frequently and was unable to retain anything by mouth for three days. The day before admission she felt better and retained some fluid. On the day of admission the pain was less severe and there was no vomiting. No stools or flatus had been passed for four days.

The abnormal findings on physical examination were confined to the abdomen and pelvis. The abdomen was distended, and there were moderate spasm and acute tenderness in the right lower quadrant. Rebound tenderness was referred to the right. There was a questionable mass in the right lower quadrant. Peristalsis was normal. Pelvic examination revealed acute tenderness in the right vault.

The temperature was 101.5°F., the pulse 108, and the respirations 22. The blood pressure was 110 systolic, 70 diastolic.

Examination of the blood showed 13 gm. of hemoglobin and a white-cell count of 23,400, with 90 per cent neutrophils. The urine gave a ++ test for albumin, and the sediment contained 40 white cells, with frequent clumps, and 6 red cells per high-power field. The nonprotein nitrogen was 15 mg. per 100 cc., and the prothrombin time 27 seconds (normal, 22 seconds).

The patient's condition remained unchanged. Dysuria developed on the second day, and there was gross blood in the urine. The temperature fell to 99°F., where it remained until the fourth hospital day, when it rose to 101.5°F. The white-cell count ranged between 19,000 and 25,000. The mass in the right lower quadrant became more definite and slightly larger.

An operation was performed on the fifth hospital day.

Differential Diagnosis

Dr. Francis Ingersoll: The outstanding fact in this case is that a septic process developed. The onset was acute and severe, and the symptoms of peritonitis rapidly developed. Fortunately, this process was localized, and when the patient was admitted on the sixth day of her illness an abscess was present in the right lower quadrant and pelvis. The elevation of the white-cell count to 23,400, with 90 per cent neutrophils, indicates an excellent response to this infection. An abscess located over the course of the ureter may lead to urinary infection with dysuria and pyuria, which were present in this case. There is no indication of whether the infection invaded the urinary tract by extension through the

lymphatic vessels or whether there was bacteremia, followed by pyelitis.

During the patient's stay in the hospital the abscess increased in size, the temperature rose, and an operation was performed on the fifth hospital day. The sequence of infection, peritonitis, localization and abscess is quite clear cut. One is left with the problem of determining the cause of the infection that initiated this series of events.

The history gives several leads: the patient was known to have had ulcerative colitis, the onset of the illness coincided with the beginning of menstruation, and with the preceding period a less severe attack had occurred. Ulcerative colitis usually bears no relation to menstruation; at the time of menstruation, however, any chronic condition may be aggravated, and there is retention of water and swelling of the pelvic organs. Partial obstruction of the diseased bowel may therefore have followed, with perforation and the development of an abscess. Against this explanation is the fact that there was no real exacerbation of the colitis. Perforation due to ulcerative colitis occurs during an acute stage of the disease.

Perforation of the bowel due to a foreign body, such as a piece of wire or a pin, often occurs in the region of the ileocecal valve, but there is nothing in the history to suggest such a possibility. Carcinoma of the cecum may perforate and give a similar picture.

Because of the radiation of the pain upward and around the flank, kidney or ureteral difficulty should be considered. Carbuncles of the kidney do not point in this direction, and stones in the ureter rarely cause abscesses, so that any genitourinary process that developed must be considered secondary to an intraperitoneal infection.

The most frequent cause of right lower-quadrant discomfort — followed in a month by a severe attack and abscess formation — is acute appendicitis with perforation. The location of this abscess was typical of one of appendiceal origin, and the history was consistent with appendicitis. On a statistical basis this case can best be explained as acute appendicitis with perforation.

Acute cholecystitis, perforating peptic ulcers and acute pancreatitis cause right lower-quadrant abscesses, but there is little in the history to suggest any of these conditions.

The fact that the pain coincided with the onset of the last two menstrual periods is stressed. This may have no significance, but it may be a lead in discovering the cause of the abscess. Infection in or around the tube or ovary, which often flares up at the time of menstruation, could account for this clinical picture. The abscesses of pelvic inflammation often localize in the right lower quadrant. Against this possibility is the statement that the patient was entirely well between the attacks of pain. The radiation of the pain is also against pelvic inflammation. Endometriosis, with secondary infection, is a rare condition that might have accounted for the abscess in this case.

My diagnosis is a right lower-quadrant abscess that was most probably secondary to an acute appendicitis.

Dr. Leland S. McKittrick: When I saw this patient in consultation at the hospital, I could not be at all certain of the diagnosis. I thought that I could feel a mass in the lower abdomen, but I was not certain because of the slight distention and the well marked tenderness. There seemed every reason to suppose that the ulcerative colitis was not responsible for this particular episode. If there was an abscess it was believed that there was everything to gain and nothing to lose by avoiding immediate operation. The patient was much better on the following day; the distention subsided, gas was freely passed by rectum, and as the abdomen softened the mass was easily palpated. At the time of operation the diagnosis was ovarian cyst with a twisted pedicle. Pelvic abscess secondary to a ruptured appendix was the second choice.

Clinical Diagnosis

Ovarian cyst, with twisted pedicle.

Dr. Ingersoll's Diagnosis

Ruptured appendix with pelvic abscess.

Anatomical Diagnosis

Dermoid cyst of ovary, with torsion and infarction.

Pathological Discussion

Dr. Benjamin Castleman: Dr. McKittrick's operative note was as follows:

> A small, right muscle-splitting incision was made, the intention being to open into any abscess that was present or to permit a diagnosis if an abscess was not encountered. When the peritoneal cavity was opened a dark mass was presented having the physical characteristics of an infarcted tumor. The incision was then enlarged, and the adherent small bowel was carefully freed. The entire mass, which proved to be an ovarian cyst with one complete rotation of the pedicle, was then freed from the abdominal wall and surrounding structures. It was removed without difficulty. No further exploration was carried out.

The specimen we received was an obviously infarcted ovarian cyst measuring 12 by 8 by 5 cm. The wall was quite thick, and the lumen was filled with the characteristic sebaceous material and hair.

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The Journal does not hold itself responsible for statements made by any contributor.

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ATOM BOMB AND MEDICAL RESEARCH

As in the case of other projects undertaken primarily for the conduct of war, many significant and far-reaching peacetime developments can be expected to result from the knowledge and materials acquired in the course of producing the atom bomb. Numerous developments of interest to biologists and to medical investigators will undoubtedly result from the fact that certain radioactive isotopes are now available in sufficient quantities for use in fundamental researches. Valuable contributions to physiology and therapeutics have already evolved as a result of the use of such isotopes produced in relatively small quantities with the cyclotron. The use of radioactive iodine in the treatment of thyrotoxicosis by Hertz and others and the studies of Ross and Gibson and their associates with radioactive iron are examples of local contributions made possible with the materials and methods developed by Evans, Roberts and others at the Massachusetts Institute of Technology.

Those in charge of the Manhattan Project* have recently made a detailed announcement concerning the isotopes that will be available and the mechanism by which investigators may obtain them. It was pointed out that the production of tracer and radiotherapeutic isotopes is one of the great peacetime contributions of the uranium chain-reaction pile. Since the inception of the pile, these men have been cognizant of its peace-time potentialities, and since the end of the war, they have been active in attempting to realize these opportunities. Since, however, the war-built piles and wartime researches had other objectives, a considerable transition in developments and operations connected with the piles must be effected before the supply of radioactive isotopes can begin to meet the demand.

The limitation of the pile in making available pure radioactive substances must be emphasized. Most of the products being made available are not salvaged by-products of the plutonium process but are items requiring special production from processed irradiated uranium. In particular, the majority of the radio isotopes in greatest demand in biology and medicine, such as those of carbon, sulfur and phosphorus, must be produced by irradiation of materials that are foreign to the existing piles, which were not designed for this purpose.

Special committees have been set up and policies have been temporarily established for the distribution of materials as they become available. The chief criterion to be used in their distribution is the maximum benefit to the national welfare considering the limited amounts of radioactive isotopes that are on hand. They are to be distributed to individuals only through qualified institutions and organizations, which will be responsible for their proper use. Charges for the additional costs incurred in filling these requests will be made to the institutions in which they are used.

A list of the supplies of the various materials on hand and their properties was published. Additional

*Availability of radioactive isotopes. Announcement from Headquarters, Manhattan Project, Washington, D. C. *Science* 103:697-705, 1946.

materials and more suitable ones will undoubtedly become available as time goes on and will probably be of the greatest help in working out many of the difficult but fundamental biologic problems that can best be solved through the use of such tracer materials. One can also look forward to considerable advances in the therapeutic use of radioactive materials.

"HIS ACTS BEING SEVEN AGES"

DR. MARJORY W. WARREN,[1] in a recent issue of the *Lancet*, has presented the case of the chronic aged sick, in whom, so often, "dull, apathetic, helpless and hopeless, life lingers on sometimes for years, while those round them whisper arguments in favour of euthanasia." This is not the picture that should be presented, nor will it be when we fully awaken to our responsibilities, which are new in their present magnitude. The aged infirm we have always had with us, but owing largely to the triumphs of medicine, the span of life has steadily lengthened, and because of the war and the entrance of women into industry, there is a shortage of young persons available to care for the aging population.

The better care of the chronic sick, and particularly the aged sick, is a medical responsibility that will in no wise decrease with time, for the expectation of life is constantly improving. Thus, in Great Britain the population of persons aged sixty or over has increased from less than 2,500,000 in 1901 to over 6,250,000 in 1944, and in the United States it is estimated that the 9,000,000 population of those sixty-five years of age or over in 1940 will increase to 22,000,000 in 1980. Since we have succeeded in prolonging human life, we must bend our energies to making that prolongation endurable. There is little doubt that the infirmities of age have been neglected and that too little effort has been made to diagnose and treat the illnesses of old people and to plan for what degree of rehabilitation may be found possible and practicable.

The aged, in their hospitalization, need wards that are designed to meet their physical circumstances, that simulate their accustomed surroundings and that are near their homes. They need diets suited to their age, and equipment adapted to their infirmities. They need floors that are not highly polished, handrails about their wards and elevators or suitably graded stairways. The geriatric hospital ward should be used as a clearinghouse to the patient's or to an otherwise suitably conducted home, with a close and continuing follow-up. Never should the patient, regardless of age, who can be salvaged for whatever time is remaining be allowed to become bedridden.

Geriatrics should be as useful a specialty for the latter end of life as pediatrics is for the beginning years. In the words of the editorial[2] accompanying Dr. Warren's paper, "Given domestic help, nursing care and medical attention when needed, many old people who now die after years in hospital could live interesting and possibly useful lives at home, finally dying triumphantly in their own beds."

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MASSACHUSETTS MEDICAL SOCIETY

BUREAU OF CLINICAL INFORMATION

All secretaries of various medical groups, such as special societies and alumni associations, are requested to notify the Bureau of Clinical Information regarding scheduled meetings, annual dinners and so forth. If such data are on file, it is hoped that duplication of dates can be avoided.

DEATHS

HARPIN — Raymond A. Harpin, M.D., of Lynn, died August 10. He was in his forty-third year.

Dr. Harpin received his degree from Boston University School of Medicine in 1931. He was a fellow of the American College of Surgeons.

His widow survives.

HOWLAND — George L. Howland, M.D., of Jamaica Plain, died August 7. He was in his seventy-seventh year.

Dr. Howland received his degree from Tufts College Medical School in 1897. He was a fellow of the American Medical Association.

LEE — Harry J. Lee, M.D., of Boston, died August 7. He was in his sixty-sixth year.

Dr. Lee received his degree from Boston University School of Medicine in 1904. He was a member of the staffs of the Newton, Cambridge and Hahnemann hospitals and the New England Hospital for Women and Children. He was a fellow of the American College of Surgeons and the American Medical Association.

His widow and two sons survive.

REID — I. Eugene Reid, M.D., of Jamaica Plain, died August 12. He was in his seventy-third year.

Dr. Reid received his degree from the University of Edinburgh Faculty of Medicine in 1897. He was a fellow of the American Medical Association.

His widow, a son and a daughter survive.

MEDICOLEGAL ABSTRACT

Relation of Patient and Physician: Liability for malpractice. The plaintiff entered the hospital in September, 1942, for rest and treatment for a nervous condition and other ailments brought about principally by acute gall-bladder attacks.

He was advised to consult the defendant, who gave him an electric shock treatment. On September 21, the defendant administered a second shock treatment. When the plaintiff recovered consciousness, he was suffering from severe pain in the right hip and thigh. This was called to the defendant's attention, but he ignored it until September 24, when x-ray examination showed a fracture of the right hip.

The plaintiff sued for negligence in the administration of the shock treatment and for negligence in the diagnosis.

At the trial the plaintiff presented no evidence other than that from which the above stated facts could be found. The defendant offered only the testimony of a doctor whom he sought to qualify as an expert on shock treatment. This witness had been an orthopedic surgeon for thirty years and had treated two hip fractures and one shoulder fracture resulting from shock treatment. He had also seen one spinal fracture resulting from shock treatment. He stated that he was familiar with the literature and reports of the medical profession on shock treatment and had talked with various specialists giving such treatment, but he admitted that he had never seen such treatment given and knew nothing of it of his own knowledge. He testified that fractures can occur in shock treatments despite every precaution taken to prevent them. The plaintiff excepted to the admission of this evidence on the grounds that the witness was not qualified as an expert on the subject of shock treatment.

The trial court ruled that there was no evidence from which a jury would be warranted in finding that the defendant had been negligent and directed a verdict for the defendant. The plaintiff excepted to this ruling, and carried both questions to the Supreme Court of Tennessee.

The plaintiff took the position that since all the equipment and instrumentalities used to administer the treatment were within the exclusive control of the defendant, it was fair to infer that his injury was the result of negligence, thus attempting to invoke the doctrine of *res ipsa loquitur*. The Court, however, decided that this doctrine is applicable only when the injury is not ordinarily explainable except by negligence — for example, when a plaintiff's eye was injured while he was unconscious during an appendectomy, or when a piece of the plaintiff's tongue was cut off in an operation for adenoids. Under such circumstances a layman could infer negligence without any explanation from an expert, but the court was of the opinion that a layman could not determine, without the help of an expert, whether or not, without negligence, a fracture could result from shock treatment. The court also gave weight to the fact that in this case the uncontradicted evidence of the expert was that such an injury could occur without negligence. (A somewhat different view of the doctrine of *res ipsa loquitur* and of the effect to be given to the fact that a patient was unconscious at the time he was injured prevailed in another case.*)

The Supreme Court decided that the witness had sufficient knowledge of medicine and medical literature to entitle him to rely on a textbook acquaintance with the subject matter of his testimony. He was qualified as an expert because he had sufficient knowledge of the subject matter, and the source of his knowledge therefore affected only the weight to be attributed to his testimony and not his qualifications to testify. (*Quinley* v. *Cocke*, 192 S.W. [2d] 992, March 2, 1946, Supreme Court of Tennessee.)

*Medicolegal abstract. *New Eng. J. Med.* 234:134, 1946.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

DISTRIBUTION OF ANTIMENINGOCOCCUS SERUM DISCONTINUED

Since the therapeutic value of sulfanilamide against meningococcal infection was first reported nine years ago,[1] it has been shown in many thousand cases that sulfonamides are the therapeutic agent of choice. As pointed out a few years ago in the *Journal*,[2] the mortality rates in groups of sulfonamide-treated cases frequently ran below 5 and rarely rose above 10 per cent — a result far superior to any that was ever obtained with serum therapy. Because of the remarkable efficacy of sulfonamide therapy in meningococcal meningitis, the Council on Pharmacy and Chemistry voted, in 1944, to omit antimeningococcus serum and meningococcus antitoxin from *New and Nonofficial Remedies*.[3] Later in the year the following editorial comment[4] was made:

> Antimeningococcus serums are still used by some medical officers and civilian physicians, perhaps because they prefer to cling to tradition or because they assume that serum therapy is an essential part of "doing everything possible." There seems to be little if any reason for believing that this supplementary form of therapy is of additional benefit. Indeed there is increasing evidence that antimeningococcus serum, particularly when given by the intrathecal route, may actually do more harm than good in most drug-treated cases.

The demand for antimeningococcus serum in Massachusetts has practically ceased in the last two years, particularly since it has been shown that penicillin is a useful supplementary remedy in patients who are unable to tolerate sulfonamides or in whom the infective strain of meningococcus is

resistant to sulfonamide therapy.[5] The Department of Public Health has therefore voted to discontinue distribution of antimeningococcus serum. In conjunction with this change in policy, it is desirable to recapitulate the principal considerations in the treatment of suspected or proved cases of meningitis.

Diagnosis. Treatment of meningitis varies according to the causative organism; specimens of cerebrospinal fluid and blood for bacteriologic examination must therefore be obtained before therapy is begun. The importance of early and accurate bacteriologic diagnosis has recently been summarized in the *Journal*.[6]

Drug therapy. In any case of meningitis in which purulent fluid is obtained by lumbar puncture, it is advisable to administer penicillin. This drug should always be given to such patients intrathecally as well as intramuscularly.

Sulfonamides (sulfadiazine, sulfamerazine and sulfathiazole) are of definite value in the treatment of meningitis caused by the pneumococcus, streptococcus or *Haemophilus influenzae* (Pfeiffer bacillus) and are the agents of choice in the treatment of meningococcal infections. Early and adequate sulfonamide therapy (by mouth, or parenterally as the sodium salt, but not intrathecally) is therefore indicated in any case of meningitis pending bacteriologic diagnosis.

Precautions. Because patients with meningitis are usually dehydrated as a result of vomiting, fever, sweating and failure to take fluids, it is essential to precede the first administration of any sulfonamide drug by the administration of fluids, given preferably by the intravenous or the subcutaneous routes and in sufficient amounts to overcome the dehydration. *Regardless of the sulfonamide drug selected or the route of administration, ample fluid output should be ensured by whatever means is most effective.* It is also advisable to administer sodium bicarbonate or lactate to prevent the precipitation of sulfonamides in the kidneys.[7] Observance of these principles will help to avert complications, which otherwise frequently arise.[8]

Specific therapy. When a bacteriologic diagnosis is established, specific therapy is recommended as follows, the agents being given in the order of preference:

Meningococcus: Sulfadiazine; penicillin.

Streptococcus: Penicillin and sulfadiazine.

Pneumococcus: Penicillin, sulfadiazine and type-specific antipneumococcus serum.*

H. influenzae (*Pfeiffer bacillus*), *Type B*: Streptomycin; sulfadiazine and anti-*H. influenzae*, Type B, serum*; all three in combination.

*Furnished by the Department of Public Health.

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CORRESPONDENCE

AN UNUSUAL FOREIGN BODY

To the Editor: Dr. Miller's report of a rose stalk in a boy's neck, in the August 1 issue of the *Journal* recalls a somewhat similar case that occurred during my internship at Worcester City Hospital more than forty years ago.

A middle-aged Polish laborer was admitted to the Accident Room with a punctured wound of the right buttock. The patient's command of English, as well as that of the friends who accompanied him, being extremely limited, no history could be elicited except that "a stick had hit him." He complained of some pain but was otherwise in good condition. The wound was explored by the finger, but since no foreign body could be felt, it was believed to be a simple puncture. He was, however, kept for observation. On the third day he developed hematuria; on the fifth day signs of general peritonitis appeared, from which he died in a few days.

Autopsy showed a piece of wood over an inch in diameter that had entered through the right sacrosciatic notch, transfixed the bladder and reached the obturator foramen on the left. Both ends were firmly fixed, and the pathologist was obliged to saw it to dislodge it from its position. It was blunt at both ends.

Later investigation showed that the patient had been working on some sort of wood-working machine when a large splinter flew off and entered his body, an extraordinary instance of centrifugal force.

PHILIP H. COOK, M.D.

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BOOK REVIEWS

The Biological Basis of Individuality. By Leo Loeb, M.D. 8°, cloth, 711 pp. Springfield, Illinois: Charles C Thomas, 1945. $10.50.

In this excellent book the author takes the position that it was necessary for one person to undertake this work, rather than to edit a collective book written by specialists in the different sciences that contribute the essential data; he appears to have succeeded admirably well in his effort. The subject is considered a mosaic of many tissues and organs, each functioning and metabolizing in its own peculiar way. The particular characteristic distinguishing one subject from another is designated as individuality differential. The author finds transplantation experiments best suited to analyzing differences as expressed in terms of individuality.

Individuality differentials on the one hand and organ and tissue differentials on the other are supported by references to comparative anatomy, embryology, genetics and biochemistry. The problems are discussed under the headings of transplantation of tissues in higher organisms, which furnishes the most delicate tests of individuality differentials; phylogenetic and ontogenetic development of individuality and organismal differentials, from the primitive to the highest organisms and from the egg to the adult state; conditions suggesting or simulating the presence of individuality differentials that exist in certain unicellular organisms; organismal differentials of tumors, which represent modified

tissues; organismal differentials in the maintenance of harmony of the organism as a whole, and in the interaction of the organs and tissues within the organism; immune processes in their bearing on the interpretation of organismal differentials; relation between the evolution of species and organismal differentials; and significance of individuality differentials in the psychosocial field — in which the concept of individuality had its origin.

There is a useful bibliography, followed by an author and subject index. This book, when read with considerable thought, will yield great profit.

The Embryology of Behavior: The beginnings of the human mind. By Arnold Gesell, M.D., Ph.D., Sc.D. In collaboration with Catherine S. Amatruda, M.D. 8°, cloth, 289 pp., with 78 illustrations, 44 plates and frontispiece. New York: Harper and Brothers, 1945. $5.00.

This book should prove to be of immense practical value to all students of human behavior. The authors develop their theme in true scientific spirit. They state: "[We attempt] to indicate how an organic complexus of behavior is built up concomitantly with the bodily development of embryo, fetus and neonate. Adopting a thoroughgoing monistic approach, we are under no necessity of defining a casual interaction between body and mind. We simply assume that as the soma takes shape, the psyche likewise takes shape. We are dealing with a single developmental morphology."

The first chapter is devoted to an instructive brief historical survey of primitive, descriptive and experimental embryology. The subsequent chapters, which are written in a clear style and are fortified by sketches and drawings, concern birth and age, zygote and embryo, genesis of behavior, the archaic motor system, the growth of fetal behavior, breathing behavior, muscle tonus, electrotonic integration, the fetal infant, the circumnatal infant, the diurnal cycle of sleep and wakeness, species and individual, the dynamic morphology of behavior and the hierarchical continuum. A striking feature of the book is a photographic delineation of behavior patterns and growth sequences. The appendix gives an example of the investigation in outline with specimen protocols.

There is a working list of selective references for each chapter, as well as a useful index. When one considers the recent effect of experimental embryology on the understanding of the constitution and the emphasis on psychosomatic medicine, one realizes that this volume is a basic contribution in this direction. It should be on the shelves of every library.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Bone-Grafting in the Treatment of Fractures. By J. R. Armstrong, M.D., M.Ch., F.R.C.S., A/W/Comm. R.A.F.M.S., and surgeon-in-charge of an R.A.F. orthopedic and fracture center, registrar to the Orthopaedic Department and to the Fracture Clinic, Charing Cross Hospital, London, and registrar to the Metropolitan Hospital, London. With a foreword by R. Watson-Jones, B.Sc., M.Ch.Orth., F.R.C.S., civilian consultant in orthopedic surgery of the Royal Air Force. 8°, cloth, 175 pp., with 204 illustrations. Baltimore: Williams and Wilkins Company, 1945. $7.00.

In this monograph the author has attempted to bring together in one volume material relating to the special subject of bone grafting in the treatment of fractures. The text is well illustrated, and there is an adequate index.

An Index of Differential Diagnosis of Main Symptoms. By various writers. Edited by Herbert French, C.V.O., C.B.E., M.A., M.D. (Oxon.), F.R.C.P., consulting physician, Guy's Hospital, assisted by Arthur H. Douthwaite, M.D., F.R.C.P., physician, Guy's Hospital. Sixth edition. 4°, cloth, 1128 pp., with 789 illustrations. Baltimore: Williams and Wilkins Company, 1945. $17.00.

This standard reference work, first published in 1912, has been fully revised, and many new laboratory tests and diagnostic methods have been included in this sixth edition. A comprehensive, inclusive index of 214 pages is appended to the text, making it possible to find in this condensed volume any subject mentioned therein. The work should be in the libraries of all general practitioners as a reference source. It is printed with a good type on filled paper, which makes it rather heavy to handle.

NOTICES

ANNOUNCEMENTS

Dr. J. Penteado Bill announces the removal of his office to the Professional Building, 270 Commonwealth Avenue, Boston.

Dr. Frank S. Broggi, having returned from military service, announces the opening of his office in Portland, Maine, for the practice of neurology and psychiatry.

Dr. Thomas G. Connelly announces the removal of offices from 676 Adams Street, Dorchester, and 270 Commonwealth Avenue, Boston, to 375 Commonwealth Avenue, Boston, for the practice of internal medicine.

Dr. Albert Y. Kevorkian announces the reopening of his office for the practice of gynecology, female urology and obstetrics at 422 Beacon Street, Boston.

Dr. Charles Gale Shedd has returned from military service and is resuming the practice of surgery at 422 Beacon Street, Boston.

Dr. L. Robert Weiss announces the removal of his office from 483 Beacon Street to 68 Bay State Road, Boston.

SUFFOLK CENSORS' MEETING

The Censors of the Suffolk District Medical Society will meet for the examination of candidates at the Boston Medical Library, 8 Fenway, on Thursday, December 5, 1946, at 4:00 p.m.

ASSOCIATION OF MILITARY SURGEONS

The convention of the Association of Military Surgeons of the United States will be held October 9 to 11, inclusive, in Detroit. Among the highlights of the meeting will be addresses by Colonel Ervin Abel, president of the association, by the Surgeons General of the United States Army, Navy and Public Health Service and by Major General Paul R. Hawley, of the Veterans Administration.

Any past or present medical, dental or veterinary officer of the United States Army, Navy, Public Health Service or Veterans Administration is eligible for membership in the association on application to the secretary, Colonel James M. Phalen, United States Army (retired), Army Medical Museum, Washington 25, D. C.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, SEPTEMBER 12

FRIDAY, SEPTEMBER 13

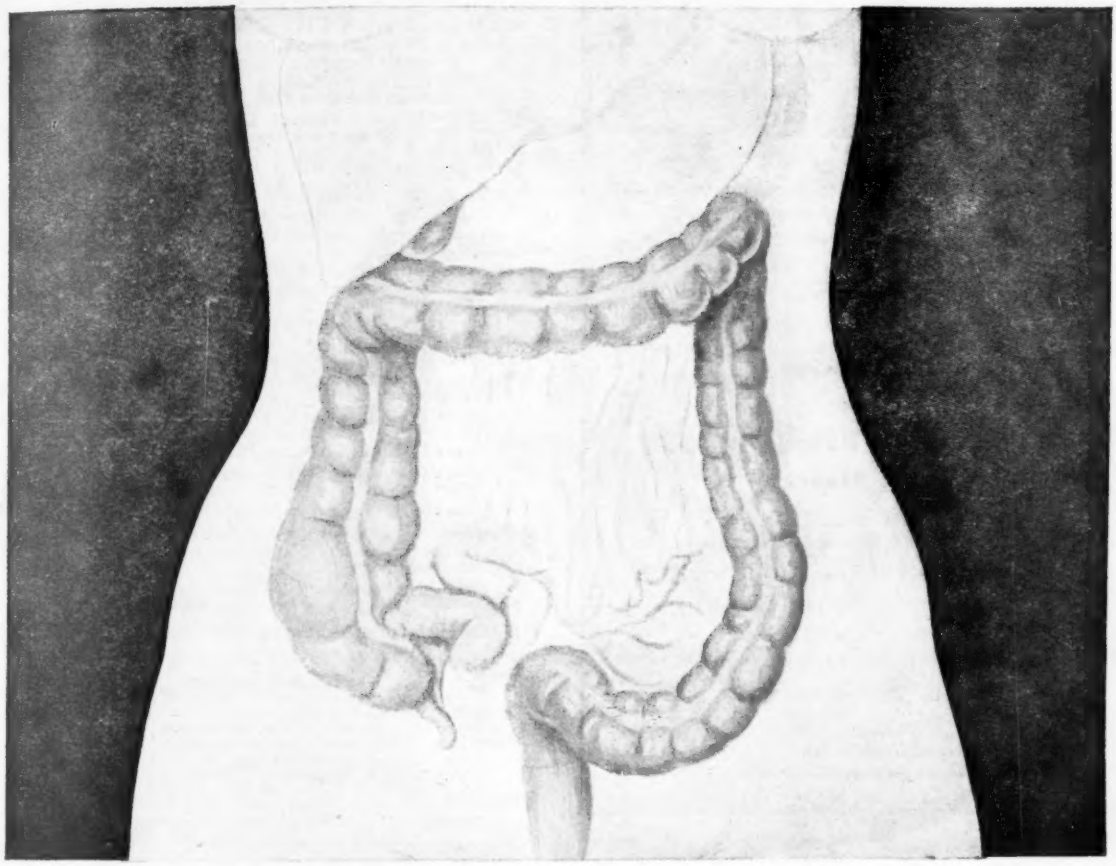
*10:00 a.m.–12:00 m. Medical Staff Rounds, Peter Bent Brigham Hospital.

12:00 m.–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

TUESDAY, SEPTEMBER 17

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

(*Notices continued on page xiv*)



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While we are, of course, constantly looking for new business of the right kind, it is never our intention to disturb satisfactory relations elsewhere. If, however, any change or increase in banking connections is contemplated, we would like very much to be kept in mind. We welcome opportunities to discuss banking or trust matters at any time.

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NOTICES (*Continued from page 346*)

WEDNESDAY, SEPTEMBER 18

*10:30–11:30 a.m. Medical Clinic. Isolation Building Amphitheater. Children's Hospital.

*12:00 m. Clinicopathological Conference. (Children's Hospital.) Amphitheater, Peter Bent Brigham Hospital.

*2:30–4:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital.

*Open to the medical profession.

MARCH 15–SEPTEMBER 15. Boston University Course for Discharged Medical Officers. Page 240, issue of February 14.

SEPTEMBER 4–7. American Congress of Physical Medicine. Page 616, issue of May 2.

SEPTEMBER 12. Bronchiectasis and Pulmonary Abscess: Diagnosis and treatment. Dr. Maurice Segal. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

SEPTEMBER 16–18. American Diabetes Association. Page 284, issue of August 22.

SEPTEMBER 23. Diabetes Clinic. Page 314, issue of August 29.

SEPTEMBER 30–October 2. Congress on Industrial Health. Page 284, issue of August 22.

OCTOBER 6–12. Interamerican Congress of Cardiology. Page xix, issue of June 6.

OCTOBER 7–12. Seminar in Legal Medicine. Page 206, issue of August 8.

OCTOBER 7–18. New York Academy of Medicine. Page 544, issue of April 18.

OCTOBER 9–11. Association for Military Surgeons. Page 346.

DECEMBER 5. Suffolk Censors' Meeting. Page 346.

FEBRUARY 7. American Board of Obstetrics and Gynecology. Page 238, issue of August 15.

APRIL 28–MAY 2. American College of Physicians. Page 206, issue of August 8.

DISTRICT MEDICAL SOCIETIES

PLYMOUTH

OCTOBER. Jordan Hospital, Plymouth.
NOVEMBER. Plymouth County Hospital, South Hanson.
JANUARY. Brockton Hospital, Brockton.
FEBRUARY. Moore Hospital, Brockton.
MARCH. Goddard Hospital, Brockton.
APRIL. State Farm, Bridgewater.
MAY. Lakeville Sanatorium, Lakeville.

SUFFOLK

DECEMBER 5. Censors' Meeting. Page 346.

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